Cardiovascular adverse effects of mAbs

Effets indésirables cardiovasculaires des anticorps thérapeutiques

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Disclosure Statement of Financial Interest

I currently have, or have had over the last two years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company:

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- Ownership/Founder: No
- Intellectual Property Rights: No

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Monoclonal antibodies (mAbs)

IgG1 (IgG2, IgG4)

Fab (Ag binding fragment)

Fc (effector functions)

CDR

FcγR

C1q

FcRn

Bejan-Angoulvant T, JESFC 2017

Courtesy Dr. D. Ternant
Mechanisms of action of mAbs

- Ligand or Receptor Antagonism
- Receptor Agonists
- Cytotoxicity: CDC or ADCC

TKI (kinase inhibitors)

Cardiovascular AE of mAbs

• Anti-HER2 : trastuzumab (HERCEPTIN)

• Anti-VEGF : bevacizumab (AVASTIN)

• Anti-immune check-point
Trastuzumab HERCEPTIN: humanized HER2 (ERBB2) antagonist

- ↑ Overall survival (HR= 0.82, p=0.004), ↑ median survival by 7–8 months
- ↑ PFS (HR 0.61, p<0.0001)

Slamon et al. NEJM 2001; Balduzzi et al. CDSR 2014
Trastuzumab: cardiac toxicity in clinical trials

Congestive heart failure (% patients)

Balduzzi et al. CDSR 2014
Trastuzumab: pathophysiology of cardiac toxicity

Investigate the role of Erbb2 in the myocardium
Mice: ventricular myocardium *Erbb2 KO* (Erbb2-CKO)

Ventricular dilation
Fœtal gene expression
Apoptosis

Récupération partielle du phénotype par injection de Bcl-xl.

*Crone et al. Nature Medicine 2002*
Trastuzumab: pathophysiology of cardiac toxicity

↓ ERK & PI3-AKT pro-oncogenic role, via BAD & BCL-2 inhibition → ↑ permeabilisation of mitochondrial membrane → apoptosis → ERBB2+ tumoral clones destruction

↓ ERK & PI3-AKT and NRG1 inhibition (role in cardiomyocytes contraction and trophicity) → ↑ permeabilisation of mitochondrial membrane → apoptosis

Hansel et al. Nature reviews 2010
Trastuzumab: risk factors of cardiac toxicity

- Concomitant or sequential chemotherapy

### Incidence and Severity of Cardiac Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>HERCEPTIN&lt;sup&gt;a&lt;/sup&gt; alone</th>
<th>HERCEPTIN+ Paclitaxel&lt;sup&gt;b&lt;/sup&gt;</th>
<th>HERCEPTIN+ Anthracycline+ cyclophosphamide&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Anthracycline+ cyclophosphamide&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 213</td>
<td>n = 91</td>
<td>n = 95</td>
<td>n = 143</td>
</tr>
<tr>
<td>Any Cardiac Dysfunction</td>
<td>7%</td>
<td>11%</td>
<td>1%</td>
<td>28%</td>
</tr>
<tr>
<td>Class III-IV</td>
<td>5%</td>
<td>4%</td>
<td>1%</td>
<td>19%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Anthracyclines + Trastuzumab -</th>
<th>Anthracyclines – Trastuzumab +</th>
<th>Sequential Therapy Anthracyclines -&gt; Trastu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiac events</td>
<td>0.97 (0.73 to 1.27)</td>
<td>1.76 (1.19 to 2.60)</td>
<td>3.96 (3.01 to 5.22)</td>
</tr>
<tr>
<td>Hospital-based CHF events</td>
<td>1.08 (0.67 to 1.74)</td>
<td>0.95 (0.45 to 2.02)</td>
<td>1.86 (1.07 to 3.22)</td>
</tr>
</tbody>
</table>

The reference group was patients receiving other chemotherapy (non-anthracyclines non–trastuzumab-based)

RCP Herceptin® FDA 1998; Thavendiranathan et al. JCO 2016
Bevacizumab (Avastin®): humanized VEGF antagonist

• IgG1, humanized, antagonizes VEGF = anti-angiogenic therapy / solid cancers, retina diseases, Rendu-Osler, ...

• Significantly increase survival in CCR, significantly improve vision,...
BUT significantly increase hemorrhagic events, arterial and venous thromboembolic events, intestinal perforations, Hypertension, ...

Reversible reduction of microvascular functional network after anti VEGF mAb therapy

Bevacizumab (Avastin®): vascular complications

**Arterial parameters**

<table>
<thead>
<tr>
<th></th>
<th>V0</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>Overall P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time frame (days)</strong></td>
<td>0</td>
<td>9.8±5.8</td>
<td>24.2±5.8</td>
<td>38.8±6.5</td>
<td>55.5±6.7</td>
<td>–</td>
</tr>
<tr>
<td><strong>Brachial SBP (mmHg)</strong></td>
<td>128±21</td>
<td>137±21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>136±15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>133±18</td>
<td>134±17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Brachial DBP (mmHg)</strong></td>
<td>74±11</td>
<td>81±12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80±11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>78±11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>78±11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Brachial mean BP (mmHg)</strong></td>
<td>95±15</td>
<td>100±15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100±11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>99±12</td>
<td>98±11</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Aortic sBP (mmHg)</strong></td>
<td>116±20</td>
<td>128±24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>124±15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>122±20</td>
<td>126±21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Aortic augmentation index @75(%)</strong></td>
<td>21±10</td>
<td>24±10</td>
<td>23±10</td>
<td>23±11</td>
<td>23±11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Heart rate (b.p.m.)</strong></td>
<td>75±14</td>
<td>73±15</td>
<td>74±13</td>
<td>74±11</td>
<td>74±13</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Pulse wave velocity (m/s)</strong></td>
<td>10.0±2.3</td>
<td>11.1±3.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.8±2.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.7±2.8</td>
<td>10.3±2.2</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Carotid stiffness (m/s)</strong></td>
<td>6.7±1.6</td>
<td>7.7±2.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.5±1.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.1±1.4</td>
<td>7.6±1.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Azizi M et al. NEJM 2008; Boutouyrie P et al. J Hypertens 2015
Bevacizumab (Avastin®): vascular complications


Anti-VEGF Therapies

- Vascular rarefaction
  - ↓Nitric oxide
  - ↓PGI, ↑ET

- Down or overexpression of renal VEGF
  - Increase of systemic vascular resistances
  - Down regulation of tight junction protein (e.g., nephrin)

Hypertension

Proteinuria

Effets vasculaires et rénaux des médicaments anti-angiogéniques : recommandations françaises pour la pratique (SN, SFHTA, APNET, FFCD)

Vascular and renal effects of anti-angiogenic therapy

Maynard SE et al. JCI 2003  Soluble fms-related tyrosine kinase 1 (sFLT1)
Antiangiogenic related Hypertension: a marker for better survival?


Bevacizumab / CCRm

## Cardiac toxicity of mAbs: Intravitreal ranibizumab+bevacizumab

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Studies</th>
<th>Patients</th>
<th>OR (Peto, fixed, 95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>12</td>
<td>4195</td>
<td>1.53 [0.92, 2.56]</td>
<td>.10</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>12</td>
<td>4195</td>
<td>1.29 [0.70, 2.37]</td>
<td>.42</td>
</tr>
<tr>
<td>Stroke</td>
<td>14</td>
<td>4368</td>
<td>1.61 [0.85, 3.05]</td>
<td>.17</td>
</tr>
<tr>
<td>rani 0.3 vs 0.5</td>
<td>9</td>
<td>4515</td>
<td>0.59 [0.34, 1.04]</td>
<td>.07</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13</td>
<td>4242</td>
<td>0.92 [0.55, 1.61]</td>
<td>.77</td>
</tr>
<tr>
<td>TVP/EP</td>
<td>5</td>
<td>1268</td>
<td>1.39 [0.17, 11.38]</td>
<td>.76</td>
</tr>
<tr>
<td>beva vs rani</td>
<td>3</td>
<td>1817</td>
<td>3.45 [1.25, 9.54]</td>
<td>.02</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>9</td>
<td>3357</td>
<td>4.39 [0.39, 49.51]</td>
<td>.23</td>
</tr>
</tbody>
</table>

*Thuillez et al. JAMA Ohpt 2014*
Immune checkpoints inhibitors
anti-CTLA4 (cytotoxic T-lymphocyte–associated antigen 4): ipilimumab
anti-PD1 (programmed death-1): pembrolizumab, nivolumab

• Self-tolerance by inhibition of auto-reactive T-cells

• Polymorphisms involved in auto-immune diseases:
  • CTLA4: Graves, Hashimoto & Addison diseases, diabetes mellitus, celiac disease, myasthenia gravis, SLE, RA
  • PD1: SLE, RA

Immune checkpoints inhibitors: immune mediated adverse effects

Immune checkpoints inhibitors: cardiac adverse effects

- myocarditis, cardiomyopathy, pericarditis, TakoTsubo, myocardial fibrosis, heart failure

- Mecanism:
  - PD1 deficient mice
    - dilated cardiomyopathy, severe impaired contraction, sudden death
  - Auto-antibodies against troponin, myocyte degeneration
  - Infiltrates with macrophages and T-cells (CD8 > CD4)
  - CTLA4 deficient mice
    - lymphoproliferative disease, multiorgan lymphocytic infiltration, severe myocarditis and pancreatitis

Tivol et al. Immunity 1995
Immune checkpoints inhibitors: immune mediated adverse effects

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

Lymphocytic Infiltration of the Myocardium

DOI: 10.1056/NEJMoa1609214

Skeletal and Smooth Muscle

Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy

Lucie Heinzerling1,2, Patrick A. Ott2, F. Stephen Hodi1, Aliya N. Husain2, Azadeh Tajmir-Riahi3, Hussein Tawbi3, Matthias Pauschinger2, Thomas F. Gajewski5, Evan J. Lipson6 and Jason J. Luke3

Heinzerling et al. Journal for ImmunoTherapy of Cancer (2016)

5/8 case-report: pre-existing cardiac pathology or PAD
### Cardiotoxicity in animal models

<table>
<thead>
<tr>
<th>Drug/Biological</th>
<th>Target(s)</th>
<th>Oncology indications</th>
<th>Preclinical cardiac findings</th>
<th>Clinical cardiac findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib (Inlyta®)</td>
<td>VEGFR1/2/3</td>
<td>RCC</td>
<td>Modest dose-dependent elevation in systolic BP in rats</td>
<td>Hypertension</td>
<td>Inlyta® FDA Pharm Review, Inlyta® Prescribing Information</td>
</tr>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>VEGF</td>
<td>CRC, NSCLC; breast cancer;</td>
<td>None reported</td>
<td>HF, hypertension, ischaemia</td>
<td>Choueiri et al. (2011), Chen et al. (2013) Avastin® Prescribing Information</td>
</tr>
<tr>
<td>Erlotinib (Tarceva®)</td>
<td>ErbB1 (EGFR)</td>
<td>RCC</td>
<td>None reported</td>
<td>Myocardial infarction/ischaemia</td>
<td>Tarceva® Prescribing Information, Kerkela et al. (2006) Gleevec® FDA Pharm Review, Gleevec® Prescribing Information</td>
</tr>
<tr>
<td>Imatinib mesylate (Gleevec®)</td>
<td>Bcr-Abl, PDGFRα and β, Kit</td>
<td>CML, ALL, GIST, MDS/MPD, ASM, HES, CEL, DFSP</td>
<td>Reversible hypertrophy in rats. Decrease in arterial BP after single i.v. dose in rats. No effect on the rate of beating or force of contraction in the isolated atria of guinea pigs</td>
<td>Decreased LVEF, LVD, rare frequency of HF</td>
<td></td>
</tr>
<tr>
<td>Lapatinib (Tykerb®)</td>
<td>EGFR (ErbB1), HER-2 (ErbB2)</td>
<td>HER-2+ ve breast cancer</td>
<td>Dose-responsive increase in BP in dog. Focal fibrosis and myocyte degeneration in rat and dog. No QT changes in rat and dog</td>
<td>Decreased LVEF, HF, asymptomatic cardiac events, QT-interval prolongation.</td>
<td>Perez et al. (2008) Tykerb® FDA Pharm Review, Tykerb® Prescribing Information</td>
</tr>
<tr>
<td>Pazopanib (Votrient®)</td>
<td>VEGFR1, VEGFR2, VEGFR3, PDGFRα/βKit</td>
<td>RCC</td>
<td>Acute increase in BP after dosing and decreased heart rate from 75 min to 24.5 h post-dose in monkeys</td>
<td>Cardiac dysfunction (congestive HF and decreased LVEF), QT prolongation, 2 cases of Torsades de Pointes in clinical programme, hypertension</td>
<td>Motzer et al. (2013) Votrient® FDA Pharm Review, Votrient® Prescribing Information</td>
</tr>
<tr>
<td>Pertuzumab (Perjeta®)</td>
<td>HER-2 (ErbB2)</td>
<td>Breast cancer</td>
<td>None reported</td>
<td>Decreased LVEF, HF</td>
<td>Perjeta® Prescribing Information</td>
</tr>
</tbody>
</table>

*Cross MJ et al. BJP 2014*
Cardiovascular adverse effects of mAbs

- Mechanism of action of mAbs incompletely known
- No pertinent preclinical models

Few mechanistic models
Clinical observational data