Complications cardio-vasculaires des traitements anti-cancéreux: hypertension pulmonaire

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FRANCE
Conflicts of Interest

- Actelion: consultancy (current), board or advisory committee (current), speaker (current)
- Bayer: consultancy (current), board or advisory committee (current), speaker (current)
- GSK: consultancy (current), board or advisory committee (current), speaker (current), research support (current)
- Novartis: consultancy (current), board or advisory committee (current), speaker (current), research support (current)
- Pfizer: consultancy (current), board or advisory committee (current), speaker (current), research support (past)
Haemodynamic definition of pulmonary hypertension

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics(^a)</th>
<th>Clinical group(s)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>PAPm ≥25 mmHg</td>
<td>All</td>
</tr>
</tbody>
</table>
| Pre-capillary PH    | PAPm ≥25 mmHg, PAWP ≤15 mmHg           | 1. Pulmonary arterial hypertension  
                           3. PH due to lung diseases  
                           4. Chronic thromboembolic PH  
                           5. PH with unclear and/or multifactorial mechanisms |
## Comprehensive clinical classification of pulmonary hypertension

### 1. Pulmonary arterial hypertension
1.1 Idiopathic  
1.2 Heritable  
   1.2.1 BMPR2 mutation  
   1.2.2 Other mutations  
1.3 Drugs and toxins induced  
1.4 Associated with:  
   1.4.1 Connective tissue disease  
   1.4.2 Human immunodeficiency virus (HIV) infection  
   1.4.3 Portal hypertension  
   1.4.4 Congenital heart diseases (Table 5)  
   1.4.5 Schistosomiasis

### 2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction  
2.2 Left ventricular diastolic dysfunction  
2.3 Valvular disease  
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies  
2.5 Congenital/acquired pulmonary veins stenosis

### 3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease  
3.2 Interstitial lung disease  
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern  
3.4 Sleep-disordered breathing  
3.5 Alveolar hypoventilation disorders  
3.6 Chronic exposure to high altitude  
3.7 Developmental lung diseases (Web Table III)*

### 4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension  
4.2 Other pulmonary artery obstructions  
   4.2.1 Angiosarcoma  
   4.2.2 Other intravascular tumors  
   4.2.3 Arteritis  
   4.2.4 Congenital pulmonary artery stenoses  
   4.2.5 Parasites (hydatidosis)

### 5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy.  
5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis  
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders  
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

*Web Table III can be found online at the journal's website.
## Drug- and Toxin-Induced PAH

### Table 7  Updated risk level of drugs and toxins known to induce pulmonary arterial hypertension

<table>
<thead>
<tr>
<th><strong>Definite</strong></th>
<th><strong>Likely</strong></th>
<th><strong>Possible</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>· Aminorex</td>
<td>· Amphetamines</td>
<td>· Cocaine</td>
</tr>
<tr>
<td>· Fenfluramine</td>
<td>· Dasatinib</td>
<td>· Phenylpropanolamine</td>
</tr>
<tr>
<td>· Dexfenfluramine</td>
<td>· L-tryptophan</td>
<td>· St John's Wort</td>
</tr>
<tr>
<td>· Toxic rapeseed oil</td>
<td>· Methamphetamine</td>
<td>· Amphetamine-like drugs</td>
</tr>
<tr>
<td>· Benfluorex</td>
<td></td>
<td>· Interferon α and β</td>
</tr>
<tr>
<td>· Selective serotonin reuptake inhibitors&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>· Some chemotherapeutic agents such as alkylating agents (mytomycin C, cyclophosphamide)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors.

<sup>b</sup>Alkylating agents are possible causes of pulmonary veno-occlusive disease.
Dasatinib-induced PAH
Dasatinib

- Tyrosine kinase inhibitor (TKI) 325 x more potent than imatinib
- Dasatinib targets BCR/ABL in patients with chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL)
- Inhibits many other tyrosine kinases including Src, c-Kit, PDGF receptor, which may be involved in PAH pathogenesis\(^1,2\)
- Side effects: pleural effusions are frequently reported

Dasatinib-induced pulmonary arterial hypertension

Lowest estimate of PH incidence:
13 cases reported in 2900 treated patients
= 0.45%

No cases reported with imatinib or nilotinib

>100 cases in Europe

Montani D, Circulation 2012
Long-Term Outcomes in Dasatinib-Induced PAH

- Mostly female (71%), median age 52
- Severe PAH at diagnosis
- Pleural effusions in 62% and pericardial effusion 29%
- Dasatinib discontinued in all patients
- Median Follow Up 24 months (range 1 – 81)
Long-Term Outcomes in Dasatinib-Induced PAH

Baseline 76% NYHA Class III or IV

Follow-Up 90% NYHA Class I or II

Baseline median 6 MWD 291 m

Follow-Up median 6MWD 435 m

Weatherald, Submitted
Long-Term Outcomes in Dasatinib-Induced PAH

Hemodynamics Improved But PAH Persists in 37%

Median PAPm improved from 46 mmHg to 26 mmHg

Median PVR improved from 6.1 to 2.6 Wood Units

Cardiac Output increased from 5.95 to 6.90 L/min
Long-Term Outcomes in Dasatinib-Induced PAH

Weatherald, Submitted
TKIs are not a therapeutic class and this term regroups drugs with very different mechanisms of action and different profile of toxicity/safety.
Hypoxic pulmonary vasoconstriction (HPV) *in vivo*

No hemodynamic changes were observed in rat chronically exposed to dasatinib

↓ Hypoxic pulmonary vasoconstriction (HPV) *in vivo*
MECHANISMS OF DASATINIB-INDUCED PAH

MCT challenge

Chronic hypoxia challenge

mPAP

Dasatinib Imatinib

mPAP

Dasatinib Imatinib

Guignabert, J Clin Invest 2016
MECHANISMS OF DASATINIB-INDUCED PAH

- Patients with CML treated with dasatinib display increased serum concentrations of sICAM-1, sVCAM-1, and sE-selectin
Dasatinib-induced pulmonary arterial hypertension

• Dasatinib is a rare cause of PAH occurring in at least 0.45% of treated patients\(^2\).

• Likely mechanism:

  mitochondrial reactive-oxygen species and a “second hit”
  ↓
  endothelial-dysfunction, injury and apoptosis\(^2\).

• Dasatinib-induced PAH is usually reversible after stopping it, however, fatal cases have occurred.\(^3\).

• Long-term hemodynamic measures indicate that hemodynamics improves after stopping it but 37% of patients show persistent PAH\(^4\).

\(^4\)Weatherald, Submitted.
Deterioration of pulmonary hypertension and pleural effusion with bosutinib following dasatinib lung toxicity

Bosutinib therapy resulting in severe deterioration of pre-existing pulmonary arterial hypertension

Pulmonary hypertension associated with ponatinib therapy
Mitomycin-induced PVOD
## 1. Pulmonary arterial hypertension

1.1 Idiopathic
1.2 Heritable
   1.2.1 Genetic
   1.2.2 Other
1.3 Drugs
1.4 Associated with:
   1.4.1 Connective tissue disease
   1.4.2 HIV infection
1.5 Others

## 1’. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1’.1 Idiopathic
1’.2 Heritable
   1’.2.1 EIF2AK4 mutation
   1’.2.2 Other mutations
1’.3 Drugs, toxins and radiation induced
1’.4 Associated with:
   1’.4.1 Connective tissue disease
   1’.4.2 HIV infection

## 1”. Persistent pulmonary hypertension of the newborn

## 2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis

## 3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases
3.4 Hypoxia
3.5 Sleep-related respiratory disorders
3.6 Other causes: interstitial lung diseases, connective tissue diseases, collagen vascular diseases, and necrotizing GPA

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*Eur Heart J 2015, Eur Respir J, 2015*
Chemotherapy-Induced Pulmonary Hypertension

Role of Alkylating Agents

Benoît Ranchoux, *† Sven Günther, *†‡ Rozenn Quarck, *‡ Marie-Camille Chaumais, *†¶ Peter Dorfmüller, *†¶ Fabrice Antigny, *† Sébastien J. Dumas, *† Nicolas Raymond, *†¶ Edmund Lau, *†‡ Laurent Savale, *†‡ Xavier Jais, *†‡ Olivier Sitbon, *†‡ Gérald Simonneau, *†‡ Kurt Stenmark, ** Sylvia Cohen-Kaminsky, *† Marc Humbert, *†‡ David Montani, *†‡ and Frédéric Perros*†

Literature analysis (1960-2014) + experience of the French PH network

<table>
<thead>
<tr>
<th>Chemotherapeutical group</th>
<th>Molecules</th>
<th>Chemotherapy-induced PVOD patients (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating or alkylating-like agents</td>
<td></td>
<td>31 (83.8%)</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide</td>
<td>16 (43.2%)</td>
</tr>
<tr>
<td></td>
<td>mitomycin</td>
<td>9 (24.3%)</td>
</tr>
<tr>
<td></td>
<td>cisplatin</td>
<td>8 (21.6%)</td>
</tr>
<tr>
<td></td>
<td>carmustine</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td></td>
<td>xarmustine</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td></td>
<td>procarbazine</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td></td>
<td>ifosfamide</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td></td>
<td>melphalan</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td></td>
<td>busulfan</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td></td>
<td>mustragan</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td></td>
<td>dacarbazine</td>
<td>1 (2.7%)</td>
</tr>
</tbody>
</table>

⇒ Cyclophosphamide and Mitomycin C : 2 animal models of PVOD

Ranchoux, *Am J Pathol 2015*
Mitomycin-Induced Pulmonary Veno-Occlusive Disease
Evidence From Human Disease and Animal Models

Frédéric Perros, PhD; Sven Günther, MD; Benoit Ranchoux, PhD; Laurent Godinas, MD; Fabrice Antigny, PhD; Marie-Camille Chaumais, PharmD, PhD; Peter Dorfmüller, MD, PhD; Aurélie Hautefort, PhD; Nicolas Raymond, MSc; Laurent Savale, MD, PhD; Xavier Jaïs, MD; Barbara Girerd, PhD; Vincent Cottin, MD, PhD; Olivier Sitbon, MD, PhD; Gerald Simonneau, MD; Marc Humbert, MD, PhD; David Montani, MD, PhD

Table. Characteristics of the 7 Patients With MMC-Induced PVOD Identified in the French PH Network

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, y</td>
<td>53</td>
<td>47</td>
<td>42</td>
<td>51</td>
<td>59</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Delay between initiation of chemotherapy and PVOD, mo</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>Mitomycin</td>
<td>Mitomycin</td>
<td>Mitomycin</td>
<td>Mitomycin</td>
<td>Mitomycin</td>
<td>Mitomycin</td>
<td>Mitomycin</td>
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<tr>
<td></td>
<td>5-FU</td>
<td>5-FU</td>
<td>5-FU</td>
<td>5-FU</td>
<td>5-FU</td>
<td>5-FU</td>
<td>5-FU</td>
</tr>
<tr>
<td>Number of cycles of mitomycin</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
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<tr>
<td>NYHA functional class, I–IV</td>
<td>IV</td>
<td>III</td>
<td>III</td>
<td>IV</td>
<td>III</td>
<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>6-MWD, m</td>
<td>Unable to perform</td>
<td>332</td>
<td>267</td>
<td>Unable to perform</td>
<td>240</td>
<td>Unable to perform</td>
<td>230</td>
</tr>
</tbody>
</table>
Mitomycin-Induced Pulmonary Veno-Occlusive Disease
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Perros, Circulation 2016
Mitomycin-induced pulmonary veno-occlusive disease

MMC-rats
Pulmonary venular remodeling
Inflammation

MMC-rats
Pulmonary capillary proliferation
Pulmonary edema

Perros, Circulation 2016
EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension

Mélanie Eyries1–3, David Montani4–6, Barbara Girerd4–6, Claire Perret3,7, Anne Leroy2, Christine Lonjou8, Nadjim Chelghoum8, Florence Coulet2,3, Damien Bonnet9,10, Peter Dorfmüller6,11, Elie Fadel6,12, Olivier Sitbon4–6, Gérald Simonneau4–6, David-Alexandre Tregouët3,7, Marc Humbert4–6 & Florent Soubrier1–3

Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study

David Montani*, Barbara Girerd*, Xavier Jais, Marilyne Levy, David Amar, Laurent Savale, Peter Dorfmüller, Andrei Seferian, Edmund M Lau, Mélanie Eyries, Jérome Le Pavec, Florence Parent, Damien Bonnet, Florent Soubrier, Elie Fadel, Olivier Sitbon, Gérald Simonneau, Marc Humbert

Summary
Background Bi-allelic mutations of the EIF2AK4 gene cause heritable pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis (PVOD/PCH). We aimed to assess the effect of EIF2AK4 mutations on the clinical phenotypes and outcomes of PVOD/PCH.
Mitomycin-induced pulmonary veno-occlusive disease

% of remodeled microvessels

GCN2

Perros, Circulation 2016
Risk factors for pulmonary veno-occlusive disease

- EIF2AK4 mutations
- Connective tissue diseases
- Chemotherapy Alkylating agents
- Solvent exposure

Oxydative stress

PVOD/PCH

Venular remodelling

Capillary proliferation
Conclusion

- Drug-induced PAH and PVOD are well recognized in the 2015 ESC/ERS pulmonary hypertension classification.
- Some tyrosine kinase inhibitors such as dasatinib have been identified as causes of (partially) reversible PAH in patients with hematologic disorders such as CML.
- Some alkylating agents such as mitomycin C have been identified as causes of irreversible PVOD.
- Pharmacovigilance is of utmost importance and one should report all signals to health authorities.