Rationale and Likely Mechanism of Action of Paclitaxel-Coated Balloons

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Disclosure

Speaker name:
Ulrich Speck

I have the following potential conflicts of interest to report:

☐ Consulting
☐ Employment in industry
☒ Stockholder of a research company
☐ Owner of a healthcare company
☒ Coinventor of several balloon coating methods

☐ I do not have any potential conflict of interest
Paclitaxel on Coated Balloons

Facts

Paclitaxel is classified as cytostatic agent; however

• intravascular dose for tumor therapy is 300 mg/adult;
• single dose of 70 mg/adult* has no recognizable adverse effects;
• maximum dose on a balloon is 1 mg (coronary) to 10 mg (peripheral);
• cytostatic effect on microtubuli is unrelated to DNA.

DCB: Where Does the Drug Go?  
(Effective Products)

<table>
<thead>
<tr>
<th>Category</th>
<th>mean [%]</th>
<th>range [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon</td>
<td>100</td>
<td>---</td>
</tr>
<tr>
<td>Lost on the way to the lesion</td>
<td>10</td>
<td>5-30</td>
</tr>
<tr>
<td>Transferred to the vessel wall</td>
<td>10</td>
<td>5-20</td>
</tr>
<tr>
<td>Lost in the blood stream during inflation</td>
<td>70</td>
<td>40-70</td>
</tr>
<tr>
<td>Paclitaxel recovered from used balloons</td>
<td>10</td>
<td>0-30</td>
</tr>
</tbody>
</table>
Paclitaxel on Coated Balloons

Facts

Mechanism

• action relies on the transfer of slowly dissolving particles into the vessel wall
Downstream Effects in Animal Experiments at High Dose

Detected in histological slices ..... 

50, S, vasculitis, 10x
40, L, scar, 10x
36, L, focal inflammation, 40x

...but no impact on myocardial function, e.g., left ventricular ejection fraction (EF) [%]

<table>
<thead>
<tr>
<th></th>
<th>3 µg/mm²</th>
<th>2 x 5µg/mm²</th>
<th>Uncoated</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>42.0±8.3</td>
<td>40.1±4.4</td>
<td>45.4±9.9</td>
<td>0.573</td>
</tr>
<tr>
<td>At 28 days</td>
<td>39.5±6.5</td>
<td>34.7±4.3</td>
<td>39.0±6.2</td>
<td>0.375</td>
</tr>
<tr>
<td>Change</td>
<td>-2.5±8.1</td>
<td>-5.4±7.0</td>
<td>-6.4±4.2</td>
<td>0.642</td>
</tr>
</tbody>
</table>
Paclitaxel on Coated Balloons

Facts

Potential particle-induced downstream effects?

• No perfusion or functional deficits in myocardium of swine in spite of multifold overdose in small hearts

• Experience with SeQuent Please in > 100 000 coronary patients: no increase in adverse effects compared to POBA or stenting

  (2014 ESC/EACTS guidelines on myocardial revascularization, Windecker et al., European Heart Journal 2014)

• Use of SeQuent Please in intracranial vessels


• Particle burden due to DCB small compared to debris shed from atherosclerotic plaques

Paclitaxel on Coated Balloons

Facts

Comparison of particle burden due to plaque debris and coated balloons

Campbell Rogers, MD et al.

Circulation 2004;109:1735-1740

- Total embolic load per lesion for filters: mean $23 \pm 19 \text{ mm}^3$, range 2 - 83 mm$^3$

- $2 - 83 \text{ mm}^3 \sim 2 - 83 \text{ mg}$

- Total Ptx content of a PTCA balloon: up to approx. 1 mg
Distal Cerebral Protection Device Filled with Calcified Plaque Debris after Carotid Stenting

Velasco A and Mosimann PJ

JACC Cardiovasc Intervent 2013; 6: 22-23
Debris after stenting of a carotid artery

Rübben et al. Interventional Cardiology, 2011
## Conclusions from Current Experience

<table>
<thead>
<tr>
<th>Study (examples)</th>
<th>Author, year</th>
<th>TLR rate 6 mths</th>
<th>TLR rate 12 mths</th>
<th>Coating-specific adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISR I + II</td>
<td>Scheller et al., 2008</td>
<td>2/54</td>
<td></td>
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</tr>
<tr>
<td>Thunder</td>
<td>Tepe et al., 2008</td>
<td>2/48</td>
<td>5/48</td>
<td>none</td>
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<tr>
<td>In.Pact Deep</td>
<td>Zeller et al. 2014</td>
<td>18/196</td>
<td></td>
<td>1?/of several</td>
</tr>
<tr>
<td>SFA II</td>
<td>Tepe et al., 2014</td>
<td>5/207</td>
<td></td>
<td>none</td>
</tr>
<tr>
<td>Levant 2</td>
<td>Rosenfield et al., 2015</td>
<td>35/285</td>
<td></td>
<td>none</td>
</tr>
</tbody>
</table>

**Conclusions**
- **Efficacy not always optimal**
- **Tolerance: no evidence of problems so far, remains to be observed**
Paclitaxel on Coated Balloons

Conclusions

Mechanism of action
• relies on the transfer of slowly dissolving particles into the vessel wall

Resulting risks
• embolic risk negligible in view of plaque debris

Room for improvement
• restenosis inhibition in >95% of patients, difficult lesions, more vessel territories
Paclitaxel on Coated Balloons

Facts

Comparison of Coronary Particle Burden due to Plaque Debris and Coated Balloons

<table>
<thead>
<tr>
<th></th>
<th>Atherosclerotic plaque material</th>
<th>DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass</td>
<td>2-83 mg</td>
<td>&lt;&lt; 1 mg</td>
</tr>
<tr>
<td>Size</td>
<td>0.015 to 20 mm²</td>
<td>?</td>
</tr>
<tr>
<td>Material</td>
<td>Extracellular matrix, lipids</td>
<td>Paclitaxel</td>
</tr>
</tbody>
</table>

Conclusion: Since embolic protection is not routinely used in coronary interventions the risk due to particles seems to be accepted?
1. „Stable“ DEB PTX coating technology

2. „Unstable“ DEB PTX coating with free PTX crystals on balloon surface
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