Toxicological aspects and safety profile of paclitaxel

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The chemistry and pharmacological properties of paclitaxel have been well characterized and studied.

- ~20 carbon atoms, a molecular weight of 853.91 g/mol.
- Highly lipophilic, and is freely soluble in common organic solvents.

**Medical uses:** Cancer / Chemotherapy, Restenosis / Anti-restenosis treatment

**Mechanism of action:** stabilization of microtubules during the final G2/M phase of cell division (apoptosis)

- IV administration requires solubilization of drug with Cremophor®
- Injected drug is immediately bioavailable in bolus or infusion
- Usually administered in multiple cycles
PTX Mechanism of Action

Paclitaxel (Cytotoxic)
*Interferes with cell division*

Cytotoxic drugs halt cell division, inducing apoptosis
Paclitaxel Pharmacokinetics

How does IV use of PTX compare to peripheral devices?
How does intravenous PTX exposure compare to DCB and DES use?

Intravenous infusion of paclitaxel for chemotherapy exhibits maximum concentration ($C_{\text{max}}$) and area under the curve (AUC) orders of magnitude higher than what is measured systemically in DCB and DES use.

3. MDT IN.PACT Admiral DCB IFU.

DCB Paclitaxel Exposure is Hundreds-fold Lower than a Single 3h Infusion for Cancer Treatment

- Area Under Curve (AUC) is the drug concentration in systemic circulation over time
- For DCBs, the concentration of bioavailable paclitaxel is **2-3 orders of magnitude lower** than in oncological application

<table>
<thead>
<tr>
<th>Drug</th>
<th>$C_{\text{max}}$ [ng/mL]</th>
<th>AUC [ng/mL*hr]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel IV 3h (180 mg/m$^2$)</td>
<td>4,468 ± 1,285</td>
<td>16,463 ± 3,757</td>
</tr>
<tr>
<td>Stellarex</td>
<td>54.4 ± 116.9</td>
<td>37.2 ± 59.2</td>
</tr>
<tr>
<td>IN.PACT Admiral</td>
<td>7.9 ± 7.7</td>
<td>29.4 ± 22.1</td>
</tr>
</tbody>
</table>

3. IN.PACT Admiral IFU, Medtronic
PTX Dosing in Cancer vs. PAD therapy

<table>
<thead>
<tr>
<th>Paclitaxel therapy / disease</th>
<th>Dosing (per course)</th>
<th>Duration</th>
<th>( C_{\text{max}} ) (plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV / Ovarian (^1)(^\dagger)</td>
<td>135 mg/m(^2)</td>
<td>3 hours</td>
<td>2170 ng/mL</td>
</tr>
<tr>
<td>IV / Ovarian (^1)(^\dagger)</td>
<td>175 mg/m(^2)</td>
<td>3 hours</td>
<td>3650 ng/mL</td>
</tr>
<tr>
<td>IV / NSCLC (^1)</td>
<td>135 mg/m(^2)</td>
<td>24 hours</td>
<td>195 ng/mL</td>
</tr>
<tr>
<td>DCB (^2)/PAD (^3)</td>
<td>4.8 mg/m(^2)</td>
<td>60 sec (DCB inflation)</td>
<td>1.6 ng/mL</td>
</tr>
</tbody>
</table>

In comparison to PTX doses for oncological treatment, maximum plasma concentration for DCB is under 1/100\(^\text{th}\) (orders of magnitude lower)

1. TAXOL Package Insert BMS Princeton, NJ Rev April 2011
2. IN.PACT Admiral 6x120mm (data on file at Medtronic)
3. Based upon animal studies (data on file at Medtronic)

\(^\dagger\) administered q 3 wks. with a median of six courses
Paclitaxel-Clopidogrel Interactions

What is the effect of clopidogrel on paclitaxel?

Can clopidogrel prolong paclitaxel metabolism?

Studies have shown that an intermediate of clopidogrel can reduce levels of an enzyme that metabolize paclitaxel.4

- Paclitaxel is primarily eliminated in the liver by the CYP2C8 enzyme.
- CYP2C8 is inhibited by metabolism of clopidogrel.
- Patients on both clopidogrel and high-dose paclitaxel (≥135mg/m^2) for chemotherapy have exhibited higher risk of neuropathy.
- At this dose, C_{max} and AUC for a 3h infusion are 2170ng/ml and 7952ng*h/ml, respectively – orders of magnitude higher than DCB use.

<table>
<thead>
<tr>
<th></th>
<th>C_{max} [ng/mL]</th>
<th>AUC [ng/mL*hr]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel IV 3h (180 mg/m^2)^1</td>
<td>4468±1285</td>
<td>16463±3757</td>
</tr>
<tr>
<td>Stellarex^2</td>
<td>54.4±116.9</td>
<td>37.2±59.2</td>
</tr>
<tr>
<td>IN.PACT Admiral^3</td>
<td>7.9±7.7</td>
<td>29.4±22.1</td>
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</table>

Additionally, the pharmacokinetic sub-study performed as part of the IN.PACT Admiral regulatory approval path included 24 of 25 patients on clopidogrel; thus the pertinent pharmacokinetic parameters, such as C_{max} and AUC already reflect the effect of clopidogrel metabolism^3

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3. MDT IN.PACT Admiral DCB IFU.

IMPACT OF PACLITAXEL COATING TYPE ON DOWNSTREAM PARTICLE EMBOLIZATION


Presented by J. Granada LINC 2017
WOUND HEALING RESPONSE AND PACLITAXEL TISSUE LEVELS

Pictures courtesy of Bob Melder, Medtronic.

Presented by J. Granada LINC 2017
EXPERIMENTAL DCB USE IN THE PRESENCE OF DISTAL LIMB WOUNDS

Wound Creation; Bilateral Treatment
PTA or DCB x1 vs. DCB x3 (5-6 mm x 80 mm)

Hollander Scoring-Margin Separation

DCB 1x versus PTA

Epithelialization nearly complete for both groups

DCB 3x versus PTA

Epithelialization nearly complete for both groups

Pictures courtesy of Bob Melder, Medtronic.

Presented by J. Granada LINC 2017
### Major Adverse Clinical Events in RCT of DCB Use in the SFA Territory

7. Presented by Jaff M, VIVA Las Vegas 2016; includes subjects of imaging cohorts: Long Lesion, CTO, and ISR.

#### 12-Month Key Safety Outcomes

<table>
<thead>
<tr>
<th>Subjects</th>
<th>LEVANT II</th>
<th>Global</th>
<th>IN.PACT SFA</th>
<th>Long</th>
<th>IN.PACT Global</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lutonix 035</td>
<td>PTA</td>
<td>IN.PACT Admiral</td>
<td>PTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>160</td>
<td>316</td>
<td>691</td>
<td>111</td>
<td>220</td>
<td>157</td>
</tr>
<tr>
<td>All Thrombosis</td>
<td>3.7% (4/107)</td>
<td>1.4% (3/207)</td>
<td>3.7% (5/134)</td>
<td>4.3% (5/115)</td>
<td>0.8% (1/124)</td>
<td>2.9% (38/1311)</td>
</tr>
<tr>
<td>Revasc. due to Thrombosis</td>
<td>0.7% (1/140)</td>
<td>0.4% (1/285)</td>
<td>1.3% (8/634)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Amputation</td>
<td>0.0% (0/140)</td>
<td>0.3% (1/286)</td>
<td>0.5% (3/635)</td>
<td>0.0% (0/107)</td>
<td>0.0% (0/207)</td>
<td>0.0% (0/134)</td>
</tr>
</tbody>
</table>

1. LEVANT II
2. Global
3. IN.PACT SFA
4. Long
5. IN.PACT Global CTO
6. IN.PACT Global ISR
7. Clinical

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**Does Distal Downstream Particle Embolization Impact Wound Healing and Could It Affect Clinical Outcomes?**

Presented by J. Granada LINC 2017
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