Toxicological Aspects and Safety Profile of Paclitaxel

Juan Granada, MD
Cardiovascular Research Foundation
Columbia University Medical Center, New York
Disclosures

Speaker name: Juan Granada, MD

I have the following potential conflicts of interest to report:

☐ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☒ Other(s): Sponsored research, advisory role.

☐ I do not have any potential conflict of interest
The Chemistry and Pharmacological Properties of Paclitaxel Have Been Fully Characterized in Humans

• **Mechanism of action**: stabilization of microtubules during the final G2/M phase of cell division
• Highly lipophilic, and is freely soluble in common organic solvents
• IV administration requires solubilization of drug with Cremophor®
• Injected drug is immediately bioavailable in bolus or infusion
• Usually administered in multiple cycles

~20 carbon atoms, a molecular weight of 853.91 g/mol.

---

1 IN.PACT Admiral IFU, 2 Taxol IFU, Bristol-Myers Squibb
**Pharmacokinetics and Pharmacodynamics of Paclitaxel are Well Characterized**

**Clinical Pharmacokinetics and Pharmacodynamics: A 3-Hour Infusion versus a 24-Hour Infusion**

Tomoko Ohtsu, Yasutsuna Sasaki, Tomohide Tamura, Yoshinori Miyata, Hiroshi Nakanomyo, Yutaka Nishiwaki, and Nagahiro Saijo

Divisions of Oncology/Hematology [O. Y., Y. S., Y. M.] and Respiratory Disease [Y. N.], Department of Medicine, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa-city, Chiba 277, Division of Respiratory Disease, Department of Medicine, National Cancer Center Hospital, Tokyo 104 [T. T., N. S.]; and Bristol-Myers Squibb K.K., Kanagawa Laboratories, Kanagawa 243-03 [H. N.], Japan

**ABSTRACT**

The present study was conducted to compare the pharmacokinetics and pharmacodynamics (PD) of paclitaxel between Phase I trials of 3- and 24-h infusions and to determine the most informative pharmacokinetic parameter to describe the PD. Twenty-seven patients were treated in a Phase I study of paclitaxel by a 3-h infusion at one of six doses, including 1-6-h (8, 9), 3-6-h (10), 9-6-h (11) infusions and 5-day continuous infusions tried. Nevertheless, at the present stage and schedule of paclitaxel regimens, no significant differences were observed. In vitro studies in several tumor cell lines were performed to determine the concentration and schedule of paclitaxel (17-19). The present study was performed with a factorial design, 2 doses (105 mg/m², 120 mg/m²), 2 infusion schedules of paclitaxel (3-h infusion or 24-h infusion). A 3-h infusion could produce a lower frequency of neuropathy. The results are shown as yet cannot be analyzed. To clear the pharmacodynamics and pharmacokinetic behaviors between these studies, data analyses are essential.

We conducted two infusions of paclitaxel with 3-h and 24-h infusions for the same dose regimen. The results are shown as yet cannot be analyzed. To clear the pharmacodynamics and pharmacokinetic behaviors between these studies, data analyses are essential.

![Graph showing concentration over time](image)

- **Typical $C_{max}$ for DCB**

<table>
<thead>
<tr>
<th>$C_{max}$ [ng/mL]</th>
<th>AUC [ng/mL*hr]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paclitaxel IV 3h (180 mg/m²)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4468±1285</td>
</tr>
<tr>
<td><strong>Stellarex</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>54.4±116.9</td>
</tr>
<tr>
<td><strong>IN.PACT Admiral</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>7.9±7.7</td>
</tr>
</tbody>
</table>

<sup>2</sup>Circulation 136: 1102-1113, Krishnan P et al.  
<sup>3</sup>IN.PACT Admiral IFU, Medtronic
Plasma Levels Following DCB Use in Human Femoro-Popliteal Arteries

Cotavance™ DCB FIH Study

- 14 patients
- Occlusion up to 5 cms
- 3 pts (2 balloons), 1 pt (3 balloons)

Number of patients with concentrations <LLOQ

Adapted from Thomas Zeller, LINC 2010.
A Variety of Organ Systems Can Be Impacted Producing a Range of Systemic Toxicities¹:

- Bone Marrow Supression
- Hypersensitivity
- Cardiovascular
- Abnormal ECG
- Peripheral Neuropathy
- Myalgia/Arthralgia
- Gastrointestinal
- Alopecia
- Hepatic
- Injection site reaction

Bone marrow suppression (primary neutropenia) is dose dependent and is the dose-limiting toxicity

¹Taxol IFU, Bristol-Myers Squibb
Non-Target Tissue Drug Concentrations (Cotavance DCB, 3.0-ug/mm²²) at 18-Months

Data on File. CRF-Skirball Center for Innovation
Non-Target Tissue Drug Concentrations are Consistently Lower than in Arteries

All non-target tissue $C_{\text{max}}$ values (distal muscle, lungs, liver, spleen, kidney) are less than 2 ng/mg for the 3X dose and 1.2 ng/mg for the nominal therapeutic dose (single 5.0 or 6.0 x 80mm IN.PACT Admiral)$^1$

$^1$LINC 2013, Medtronic, R. Melder
Paclitaxel Particulate Downstream Effect


Paclitaxel Particle and Wound Healing

Granada JF, TCT2018
Consideration of Factors Relevant to DCBs

- Paclitaxel use may induce a constellation of toxicities which are usually dose and schedule dependent:
  - A single DCB use results in a small fraction of bioavailable drug at any time\(^1\) compared to the IV infusion of Paclitaxel for cancer therapy which involves multiple cycles\(^2,\,^3\)
  - Systemic Paclitaxel exposure post DCB use is several orders of magnitude lower than that of a single cycle of drug infusion\(^2,\,^3\)
  - Multi-organ distribution and concentration of Paclitaxel resulting from DCB use is lower and more transient than at the target site\(^4\), limiting exposure of systemic tissues
  - Understanding the role of drug-induced toxicity in mediating treatment-associated mortality requires a careful and rational examination of dosing and exposure in the context of the known pharmacology of Paclitaxel

\(^1\)Journal Drug Delivery Volume 2019, Article ID 9560592 Granada, J et al. \(^2\)Taxol IFU, Bristol-Myers Squibb, . \(^3\)IN.PACT Admiral IFU; Circulation 136: 1102-1113, Krishnan P et al. \(^4\)LINC 2013 Review, Melder R
Toxicological Aspects and Safety Profile of Paclitaxel

Juan Granada, MD
Cardiovascular Research Foundation
Columbia University Medical Center, New York