Model-Based Meta-Analysis for the Efficacy and Safety of Paclitaxel in Cancer Patients

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Background

Drug Development Paradigm

Knowledge accumulation through each learn and confirm cycle

Preclinical Studies  Human Phase 1  Human Phase 2  Human Phase 3

Knowledge Burst from Historical Data

Preclinical Studies  Human Phase 1  Human Phase 2  Human Phase 3

Historical Compounds

Graph modified from Zhang L et al. JPP. 33(3) 2006
Objectives

Paclitaxel in Breast Cancer

- The recommended Paclitaxel (PAC) dosing is 175 mg/m² q3w for metastatic breast cancer (mBC) on the label.
- Current clinical practice of PAC dosing is 65-90 mg/m² qw for mBC*
- Multiple NMEs are in development in combination with PAC, or using PAC as active control arm

PROBLEM STATEMENT:
- Collection of PAC efficacy, safety, and PK data after monotherapy is needed for better data interpretation of combination trials with NME.
- Better understanding the dose-response relationships would also help selection of the right PAC dose and regimen for combination trials or as active control arm.

*Sparano JA et al. NEJM. 2008; 358 (16): 1663
Methods

Model-Based Meta-Analysis of Paclitaxel

- The PAC monotherapy literature database was established based on thorough literature review.
  - Efficacy in mBC (OS, PFS, TTP, OR, type of responder……)
  - Safety in mBC, mixed, or others (neutropenia, febrile neutropenia, leukocytopenia, thrombocytopenia, WBC count, neutrophil count, platelet count……)
  - PK (concentration, AUC, CL, V<sub>ss</sub>, t<sub>1/2</sub>……)

- PAC dose-response relationship developed for:
  - [Efficacy] Objective Response (mBC)
  - [Efficacy] Overall Survival (mBC)
  - [Safety] Neutropenia (all)
Results

Overview of the Paclitaxel Literature Database

- The PAC monotherapy literature database was developed based on summary-level data from 55 publications of 49 trials with 95 arms of 4256 patients.

Dosing Frequency

<table>
<thead>
<tr>
<th></th>
<th>q3w</th>
<th>qw</th>
<th>Single Dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Trials</td>
<td>33</td>
<td>19</td>
<td>2</td>
<td>49</td>
</tr>
<tr>
<td>Breast/Mixed or Others</td>
<td>22/13</td>
<td>14/5</td>
<td>1/1</td>
<td>35/16</td>
</tr>
<tr>
<td>Efficacy/Safety/PK</td>
<td>19/28/17</td>
<td>14/18/6</td>
<td>0/2/2</td>
<td>31/44/22</td>
</tr>
<tr>
<td>N Arms</td>
<td>67</td>
<td>23</td>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>N Patients</td>
<td>2938</td>
<td>1283</td>
<td>35</td>
<td>4256</td>
</tr>
</tbody>
</table>

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Graph modified from Quantitative Solutions, Inc.
Objective Response of Paclitaxel in mBC

Results

- Trend of better OR with average dose (mg/m²/wk), but not with administered dose (mg/m²)

- 29 trials with 35 arms of 3070 mBC pts:
  - %Patients with partial or complete response vs. PAC dose (mg/m²) or average dose (mg/m²/wk).
  - Symbols are observed data from literature with symbol size representing arm size, n = 15-258.
**Results**

**Modeling of Objective Response**

Logistic regression with linear dose effect:

\[
\text{Logit}(\%OR_{ij}) = \text{Intercept} + \text{Slope} \times \text{DOSE}_{ij} + \omega_i + \epsilon_{ij}
\]

DOSE — average PAC dose in mg/m²/wk;
\(\omega_i\) — inter-trial variability;
\(\epsilon_{ij}\) — residual variability;
i\text{th} trial, j\text{th} arm
Covariates tested — regimen, prior chemo (Y/N)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate*</th>
<th>%RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-1.62</td>
<td>34.2</td>
</tr>
<tr>
<td>Slope</td>
<td>0.0133</td>
<td>52.4</td>
</tr>
<tr>
<td>Inter-trial variability (Sd of (\omega))</td>
<td>0.489</td>
<td>20.6</td>
</tr>
<tr>
<td>Residual variability (Sd of (\epsilon))</td>
<td>2.14</td>
<td>27.3</td>
</tr>
</tbody>
</table>

* S-Plus v6.2
Results

Modeling of Objective Response

- %OR best correlated with average PAC dose (linear model). This result implied PAC efficacy may be driven by overall exposure.
- No COV effect (regimen, prior chemo)

Application example:
- Increase of PAC dose from 60 to 90 mg/m^2/wk qw (ie. 180 to 270 mg/m^2 q3w) may increase the %OR from 30.5% (95%CI: 25.3-36.2%) to 40.0% (95%CI: 34.9-44.8%) in a typical mBC trial.

- Line and shading are predicted median and 90%CI of the dose-response relationship.
- Symbols are observed data from literature with symbol size representing arm size, n = 15-258.


**Results**

**Overall Survival of Paclitaxel in mBC**

- **Trend of better OS for qw than q3w**
- **Trend of better median OS with average dose (mg/m²/wk), but not with administered dose (mg/m²)**

15 trials with 19 arms of 2749 mBC pts: median OS vs. PAC dose (mg/m²) or average dose (mg/m²/wk).

Symbols are observed data from literature with symbol size representing arm size, n = 30-326.
Results

Modeling of Overall Survival

Proportional hazard model with linear dose effect:

\[ S(t_k) = S(t_k)_{rf}^{RR_{ij}} \]

\[ \text{Logit}(RR_{ij}) = \text{Intercept} + \text{Slope} \times \text{DOSE}_{ij} + \omega_i + \epsilon_{ik} \]

RR — relative risk;
DOSE — average PAC dose in mg/m²/wk;
\( \omega_i \) — inter-trial variability;
\( \epsilon_{ij} \) — residual variability;
i\text{th} trial, j\text{th} arm, k\text{th} time
Covariates tested — regimen, prior chemo (Y/N)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate*</th>
<th>%RSE</th>
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<tr>
<td>Intercept</td>
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<td>1.8</td>
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<td>Slope</td>
<td>-0.0199</td>
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<tr>
<td>Inter-trial variability (Sd of ( \omega ))</td>
<td>0.214</td>
<td>27.8</td>
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<tr>
<td>Residual variability (Sd of ( \epsilon ))</td>
<td>1.15</td>
<td>23.5</td>
</tr>
</tbody>
</table>

* S-Plus v6.2
Results

Modeling of Overall Survival

- Observed (open circle) and predicted (median w 95%CI) survival of individual trials
Results

Modeling of Overall Survival

- Line and shading are predicted median and 95%CI for median OS.
- Symbols are observed data from literature with symbol size representing arm size, n = 30-326.

- Relative risk of OS best correlated with average PAC dose (linear model). This result implied PAC efficacy may be driven by overall exposure.
- No COV effect (regimen, prior chemo)

Application example:
- Increase of PAC dose from 60 to 90 mg/m2/wk qw (180 to 270 mg/m2 q3w) may increase median OS from 11.1 m (95%CI: 7.2-17.8 m) to 20.6 m (95%CI: 13.1-32.2 m) in a typical mBC trial.
Neutropenia of Paclitaxel

- Trend of less neutropenia for qw than q3w
- Trend of more neutropenia with administered dose (mg/m²), but not with average dose (mg/m²/wk)

**Results**

- 24 trials with 35 arms of 1886 pts:
- % Patients with Grade 2, 3, or 4 neutropenia vs. PAC dose (mg/m²) or average dose (mg/m²/wk).
- Symbols are observed data from literature with symbol size representing arm size, n = 3-255.
Results

Modeling of Neutropenia

Logistic regression with saturable dose effect:

\[
\text{Logit} \left( \% \text{NeuP}_ij^{Gr2,3,4} \right) = \text{Intercept} + \frac{E_{\text{max}} \times \text{DOSE}_{ij}}{\text{ED}_{50} + \text{DOSE}_{ij}} + \omega_i + \varepsilon_{ij}
\]

- \( \text{DOSE} \) — administered PAC dose in mg/m²;
- \( \omega_i \) — inter-trial variability;
- \( \varepsilon_{ij} \) — residual variability;
- \( i^{th} \) trial, \( j^{th} \) arm

Covariates tested — regimen, prior chemo (Y/N), treatment duration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate*</th>
<th>%RSE</th>
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</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-5.51</td>
<td>20.1</td>
</tr>
<tr>
<td>( E_{\text{max}} )</td>
<td>9.2 (fix)**</td>
<td>-</td>
</tr>
<tr>
<td>( \text{ED}_{50} )</td>
<td>70.1</td>
<td>12.9</td>
</tr>
<tr>
<td>Inter-trial variability (Sd of ( \omega ))</td>
<td>0.577</td>
<td>20.9</td>
</tr>
<tr>
<td>Residual variability (Sd of ( \varepsilon ))</td>
<td>2.2</td>
<td>27.6</td>
</tr>
</tbody>
</table>

* S-Plus v6.2; ** Fix to 100% Neutropenia (99.9% on logit scale)
Results

Modeling of Neutropenia

- %Neutropenia best correlated with administered PAC dose (Emax model). This result implied PAC safety may be driven by Cmax.
- No COV effect (regimen, prior chemo, treatment duration)

Application example:
- Observed neutropenia rate after NME + PAC in Phase Ib is consistent with historical PAC monotherapy safety, suggesting no decreased tolerability with the combination therapy.

- Yellow circle is observed data from Phase Ib with symbol size representing arm size, n = 36.
- Line and shading are predicted median and 90%CI of the dose-response relationship.
- Symbols are observed data from literature with symbol size representing arm size, n = 3-255.
The recommended Paclitaxel (PAC) dosing is 175 mg/m² q3w for metastatic breast cancer (mBC) on the label.

Current clinical practice of PAC dosing is 65-90 mg/m² qw for mBC

Paclitaxel 65-90 mg/m² qw is projected to have similar-better efficacy and much better tolerability than 175 mg/m² q3w.
Model-Based Meta-Analysis

- The effect of PAC dose and regimen on clinical efficacy and safety was quantified by model-based meta-analysis integrating literature data from multiple trials.

- These analyses can be used to guide trial design and interpretation for PAC as control agent or as combination therapy with new anti-cancer agents.

- Strategic development and application of these modeling and simulations platforms could lead to more effective drug development across projects.