Cystatin C 
as a new covariate to
predict drugs renal elimination

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Cystatin C

- Small Protein (120 amino-acids) expressed in all nucleated cells. Inhibitor of cysteine proteases.
- Marker of Glomerular Filtration Rate (GFR)
  - Glomerular filtration +++
  - Not secreted
  - Completely reabsorbed and catabolised
- Independent on age, gender, muscle mass.

→ Conflicting results about cystatin’s performance compared to creatinine...

→ Cystatin and digoxin clearance (O’Riordan et al. Br J Clin Pharmacol, 2002) → not better
Carboplatin
- Mainly eliminated by glomerular filtration
- Carboplatin clearance predicted by several formulae including serum creatinine level
- Cystatin: new covariate for individual dosing?

Thomas et al, Clin Pharmacokinet 2005

Topotecan
- Renal elimination accounts for 50% of the total elimination
- Its clearance is correlated with creatinine clearance
- If Cl\text{\textsubscript{creat}}>39ml/min: 1.5mg/m\textsuperscript{2}
- If 20<Cl\text{\textsubscript{creat}}<39ml/min: 0.75mg/m\textsuperscript{2}
- Cystatin: new covariate for prediction of topotecan clearance?

Hoppe et al, Clin Cancer Res 2005

$^{51}$Cr-EDTA
- Direct measure of GFR by determination of $^{51}$Cr-EDTA plasma concentrations after a bolus dose.
- Children (1.4 to 21.4 years)
- GFR estimated by Schwartz formula (serum creatinine, height, coefficient specific of the laboratory)
- Cystatin: new covariate for GFR estimation?

Bouvet et al, Ped Nephrol in press 2006
Methods (1)

**Carboplatin study**
- 45 patients
- Sparse data of ultrafilterable plasma concentration
- Database = 188 patients

**Topotecan study**
- 59 patients
- Topotecan data

**$^{51}$Cr-EDTA study**
- 100 children
- 4 samples

1) Run without covariates
   - NONMEM analysis
   - Two-compartment model
   - FOCE
   - Proportional error model

POSTHOC clearance = $C_l_{\text{actual}}$
Methods (2)

Carboplatin study
- 45 patients

Topotecan study
- 59 patients

\(^{51}\)Cr-EDTA study
- 100 children

DATA SPLITTING

*Model Building Data Set* → 2/3 of patients

*Validation Data Set* → 1/3 of patients

Find the best covariates models

Prospective validation of models
Validation data set

**TVCL = θ₁**

→ 

OFV and IIV

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**Model building data set**

**Covariate analyses**

- $\text{Scr (serum creatinine)}$
- $\text{CysC (serum cystatin C)}$
- $\text{Alb, Sun, Age, sex, PS}$
- $\text{BW (body weight), IBW, BSA}$

$\text{TVCL} = \theta_1 \cdot \left( \frac{\text{cov}}{\text{mean(cov)}} \right)^{0.5}$  \(\Delta \text{OFV, } \Delta \text{ IIV}\)

$\text{TVCL} = \theta_1 \cdot \left( \frac{\text{cov1}}{\text{mean(cov1)}} \right)^{0.2} \cdot \left( \frac{\text{cov2}}{\text{mean(cov2)}} \right)^{0.3}$  \(\Delta \text{OFV, } \Delta \text{ IIV}\)

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**INTERMEDIATE MODEL**

**Validation data set**

**FINAL MODEL**

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**Methods (3)**

Stepwise backward elimination
Carboplatin (1)

**Scr** = serum creatinine

**CysC** = serum cystatine C
### Final covariate model

<table>
<thead>
<tr>
<th>( \text{CL (mL/min)} )</th>
<th>( = )</th>
<th>113</th>
<th>( \left( \frac{\text{BW}}{65} \right)^{0.463} \cdot 0.85^{\text{sex}} )</th>
<th>( \left( \frac{\text{SCr}}{75} \right)^{0.399} \cdot \left( \frac{\text{CysC}}{1} \right)^{0.306} \cdot \left( \frac{\text{age}}{56} \right)^{0.407} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{IIV} )</td>
<td></td>
<td>14%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Alternative models

<table>
<thead>
<tr>
<th>( \text{CL (mL/min)} )</th>
<th>( = )</th>
<th>112</th>
<th>( \left( \frac{\text{BW}}{65} \right)^{0.331} \cdot 0.86^{\text{sex}} )</th>
<th>( \left( \frac{\text{CysC}}{1} \right)^{0.507} \cdot \left( \frac{\text{age}}{56} \right)^{0.369} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \text{OFV} )</td>
<td></td>
<td>+6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{P} )</td>
<td></td>
<td>&lt;0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{IIV} )</td>
<td></td>
<td>16%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>( \text{CL (mL/min)} )</th>
<th>( = )</th>
<th>110</th>
<th>( \left( \frac{\text{BW}}{65} \right)^{0.625} \cdot 0.90^{\text{sex}} )</th>
<th>( \left( \frac{\text{SCr}}{75} \right)^{0.654} \cdot \left( \frac{\text{age}}{56} \right)^{0.507} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \text{OFV} )</td>
<td></td>
<td>+6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{P} )</td>
<td></td>
<td>&lt;0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{IIV} )</td>
<td></td>
<td>16%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Carboplatin (3)

→ Prospective validation: predicted vs. actual CL

<table>
<thead>
<tr>
<th></th>
<th>Scr</th>
<th>CysC</th>
<th>Scr and CysC</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R^2 )</td>
<td>0.70</td>
<td>0.72</td>
<td>0.80</td>
</tr>
<tr>
<td>MAPE (%)</td>
<td>17%</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>Mean Absolute Percentage of Error</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPE (%)</td>
<td>+11%</td>
<td>+6%</td>
<td>+7%</td>
</tr>
<tr>
<td>Mean Percentage of Error</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Carboplatin (4)

→ Whole data set: predicted vs. actual CL

y = 0.84x + 14.4
R² = 0.77

Calculated CL with the final model (5 covariates) (mL/min)

Actual CL (mL/min)

model building data set
validation data set

\[ y = 0.84x + 14.4 \]

\[ R^2 = 0.77 \]
### Topotecan (1)

<table>
<thead>
<tr>
<th>Equation to estimate topotecan clearance (L/h)</th>
<th>IIV</th>
<th>OFV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intermediate model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{CL} = 20.1 \cdot \frac{\text{IBW}/57}{57}^{0.98} \cdot \frac{\text{age}/57}{57}^{0.001} \cdot \left( \frac{\text{CysC}/1.06}{1.06} \right)^{0.52} \cdot \left( \frac{\text{Scr}/85.2}{85.2} \right)^{0.14} )</td>
<td>23%</td>
<td>480.2</td>
<td></td>
</tr>
<tr>
<td><strong>Final models</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \boxed{\text{CL} = 20.2 \cdot \frac{\text{IBW}/57}{57}^{0.95} \cdot \left( \frac{\text{CysC}/1.06}{1.06} \right)^{0.6} } )</td>
<td>23%</td>
<td>480.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( \boxed{\text{CL} = 20.2 \cdot \frac{\text{IBW}/57}{57}^{1.23} \cdot \left( \frac{\text{Scr}/85.2}{85.2} \right)^{0.52} } )</td>
<td>26%</td>
<td>490.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Topotecan (2)

→ Whole data set: predicted vs. actual CL

\[ y = 0.91x + 2.8 \]
\[ R^2 = 0.23 \]

\[ y = 1.0x + 0.6 \]
\[ R^2 = 0.43 \]
### Equation to estimate $^{51}$Cr-EDTA clearance (mL/min)

<table>
<thead>
<tr>
<th>Equation</th>
<th>IIV</th>
<th>ΔOFV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Final model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{CL} = 62.8 \times \frac{(BW/45)^{0.33} \times (age/14)^{0.36}}{(Scr/96)^{0.41} \times (CysC/1.2)^{0.49}}$</td>
<td>19%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Alternative models</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{CL} = 62.6 \times \frac{(BW/45)^{0.33} \times (age/14)^{0.22}}{(CysC/1.2)^{0.82}}$</td>
<td>22%</td>
<td>+16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$\text{CL} = 64 \times \frac{(BW/45)^{0.23} \times (age/14)^{0.52}}{(Scr/96)^{0.76}}$</td>
<td>24%</td>
<td>+19</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
**Prospective validation: predicted vs. actual CL**

\[
CL = 62.8 \cdot \frac{(BW/45)^{0.33} \cdot (age/14)^{0.36}}{(Scr/96)^{0.41} \cdot (CysC/1.2)^{0.49}}
\]

<table>
<thead>
<tr>
<th></th>
<th><strong>Final model</strong></th>
<th><strong>Schwartz</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>( R^2 )</td>
<td>0.59</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>MAPE (%)</strong></td>
<td>17.4</td>
<td>17.3</td>
</tr>
<tr>
<td><strong>MPE (%)</strong></td>
<td>+0.9</td>
<td>-8.2</td>
</tr>
<tr>
<td><strong>Min % error</strong></td>
<td>-45</td>
<td>-62</td>
</tr>
<tr>
<td><strong>Max % error</strong></td>
<td>+44</td>
<td>+431</td>
</tr>
</tbody>
</table>

\[ GFR = k \cdot \frac{\text{height}}{\text{Scr}} \]
$\text{^{51}Cr-EDTA (3)}$

→ Whole data set: predicted vs. actual CL

\[
y = 0.84x + 12.4 \\
R^2 = 0.59
\]

\[
y = 1.20x - 12.3 \\
R^2 = 0.72
\]
Inter individual variability
(whole data set, $R^2$)

Carboplatin

- CysC + Scr
- 71%
- 77%

Topotecan

- CysC + Scr
- 43%
- 71%
- 41%

GFR

- CysC + Scr
- 69%
- 59%
- 72%
Conclusions

- Cystatine C is a better covariate than creatinine to predict drug renal clearance.
- **Limits:**
  - Should be studied with others covariates (BW, age...)
  - 2.51 euros/analysis versus 0.03 euros for creatinine.
- **Advantages:**
  - Nephelometric immunoassay (Dade-Behring) less variable than creatinine (Jaffé vs. Enzymatic)
  - Superiority over creatinine larger at a multicenter level
  - Likely to be more adapted for equation-based dose adjustment