Prospective Bayesian pharmacokinetically guided dosing of cyclophosphamide, thiotepa and carboplatin in high-dose chemotherapy

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INTRODUCTION

Pharmacokinetically guided dosing or Therapeutic Drug Monitoring:

The use of drug concentration measurements in plasma or other biological fluids to assist in determination of drug dosage for the individual patient

Goal: to provide safe, therapeutic doses in order to improve drug efficacy and reduce toxicity
INTRODUCTION

Requirements:

- narrow therapeutic index
- substantial interpatient pharmacokinetic variability
- relationship between plasma drug concentration and therapeutic effect or toxicity
- steep relationship between exposure and response
- relatively small intraindividual variability
- available assay for quantification
- available dose adaptation strategy
INTRODUCTION

High-dose CTC chemotherapy:

- Cyclophosphamide 1500 mg/m²/day
- Thiotepa 120 mg/m²/day
- Carboplatin 400 mg/m²/day or
  AUC=5 mg*min/mg/day during 4 days

tCTC= 2/3 of total CTC dose
INTRODUCTION

Toxicity in the CTC regimen:

Gastro-intestinal: nausea, vomiting, mucositis, diarrhea
Hemorrhagic cystitis
Veno-occlusive disease of the liver (VOD)
Cardiac toxicity
Sensory neuropathy
Hearing loss
Renal failure
Skin rash
OBJECTIVE

Primary goal:
To investigate whether pharmacokinetically guided dosing of cyclophosphamide, thiotepa and carboplatin reduces the variability in exposure to these compounds

Secondary goal:
To investigate the clinical effect of targeted drug dosing in the CTC regimen
DESCRIBING PHARMACOKINETICS

Population pharmacokinetics:

- data available of 43 patients receiving CTC (65 courses)
- multiple samples during and after CTC (approx. 21 samples / course)
- modeled using NONMEM
Exposure to carboplatin has been correlated with nephro-, oto- and central nervous system toxicity.
Exposure to thiotepa and tepa have been correlated with elevation of transaminases and mucositis.
DESCRIBING PHARMACOKINETICS

cyclophosphamide

\[
\begin{align*}
\text{cyclophosphamide} & \rightarrow \text{2-dechloroethylcyclophosphamide} + \text{chloroacetaldehyde} \\
\text{4-hydroxycyclophosphamide} & \rightarrow \text{aldophosphamide} \\
\text{aldophosphamide} & \rightarrow \text{carboxyphosphamide} \\
\text{phosphoramide mustard} & + \text{acrolein}
\end{align*}
\]
Exposure to cyclophosphamide has been inversely correlated with cardiotoxicity. Exposure to 4-hydroxy-cyclophosphamide has been correlated with VOD.
DEFINING SUITABLE TARGET EXPOSURES

Definitive safe and effective target exposure not established
Optimal exposure = median AUC of reference population

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC tCTC</th>
<th>AUC CTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-hydroxycyclophosphamide</td>
<td>105 µM*h</td>
<td>140 µM*h</td>
</tr>
<tr>
<td>thiotepa + tepa</td>
<td>276 µM*h</td>
<td>374 µM*h</td>
</tr>
<tr>
<td>carboplatin</td>
<td>13.3 mg*min/ml</td>
<td>20 mg*min/ml</td>
</tr>
</tbody>
</table>
STUDY DESIGN

COURSE 1

DAY1 | DAY2 | DAY3 | DAY4

Standard dose + bloodsampling

Adapted dose + bloodsampling

drug analysis

COURSE 2

DAY1 | DAY2

Adapted dose + bloodsampling

Adapted dose + bloodsampling

drug analysis

etc.

NKI-AVL

Het Nederlands Kanker instituut
Antoni van Leeuwenhoek Ziekenhuis
Simultaneous quantification of cyclophosphamide, 4-hydroxycyclophosphamide, thiotepa and tepa using LC-MS/MS
## RESULTS

Dose adaptations in 46 patients, 108 courses

*Number of performed dose adaptations*

<table>
<thead>
<tr>
<th></th>
<th>Between courses</th>
<th>During courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>17x</td>
<td>39x</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>40x</td>
<td>58x</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>43x</td>
<td>65x</td>
</tr>
</tbody>
</table>
RESULTS

During courses

Carboplatin

Thiotepa

Cyclophosphamide

Between courses

CD PKD CD PKD

30 13 31 19

36 16 57 32

29 19 23 19

31 19

57 32

23 19

Precision (%)
## RESULTS

<table>
<thead>
<tr>
<th>Adaptations</th>
<th>Exposures within $\pm 25%$ of target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PKD</td>
</tr>
<tr>
<td><strong>Carboplatin</strong></td>
<td></td>
</tr>
<tr>
<td>During courses $(n=65)$</td>
<td>62 (95%)</td>
</tr>
<tr>
<td>Between courses $(n=43)$</td>
<td>35 (81%)</td>
</tr>
<tr>
<td><strong>Thiotepa</strong></td>
<td></td>
</tr>
<tr>
<td>During courses $(n=58)$</td>
<td>52 (90%)</td>
</tr>
<tr>
<td>Between courses $(n=40)$</td>
<td>28 (70%)</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td></td>
</tr>
<tr>
<td>During courses $(n=39)$</td>
<td>33 (85%)</td>
</tr>
<tr>
<td>Between courses $(n=17)$</td>
<td>13 (76%)</td>
</tr>
</tbody>
</table>
# RESULTS

<table>
<thead>
<tr>
<th>Toxic event</th>
<th>Reference patients (n=43)</th>
<th>Patients receiving adapted doses (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOD</td>
<td>2 (5%)</td>
<td>3 (7%)a</td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>2 (5%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Cardiotoxicity ≥ grade 1</td>
<td>3 (7%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Pulmonary toxicity ≥ grade 1</td>
<td>6 (14%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Mucositis ≥ grade 3</td>
<td>6 (14%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Neuropathy ≥ grade 3</td>
<td>0 (0%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Ototoxicity ≥ grade 2</td>
<td>9 (21%)</td>
<td>22 (24%)</td>
</tr>
</tbody>
</table>

*a none of these patients received an adjusted dose of cyclophosphamide*
CONCLUSIONS

• Pharmacokinetically guided dosing of cyclophosphamide, thiotepa and carboplatin results in reduction of variability in exposures

• Extremely high exposures are effectively prevented

• More patients should be included to draw significant conclusions on the clinical impact of the dosing strategy
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