Population K-PD joint modeling of tumor size and CA 125 kinetics after chemotherapy in relapsed ovarian cancer (ROC) patients


TherapeuticiC Targeting in Oncology - EMR 3738 - Faculty of medicine Lyon Sud, France
University Claude Bernard Lyon 1

21st PAGE meeting

June 7th, 2012
Background

Ovarian cancer (OC):

- Highest mortality rate among all gynecological cancers
- Majority of patients diagnosed at an advanced stage
- Primary debulking surgery followed by chemotherapy
- Majority of patients relapses

Mélanie Wilbaux

Tumor size and CA 125 kinetics modeling - PAGE 2012
Background

Ovarian cancer (OC):

- Highest mortality rate among all gynecological cancers
- Majority of patients diagnosed at an advanced stage
- Primary debulking surgery followed by chemotherapy
- Majority of patients relapses

→ Reliable clinical strategy for early prediction of treatment efficacy, tumor dynamics, and tumor resectability
Background

CA 125 (*Cancer Antigen*):
- Serum marker of epithelial ovarian cancers
- Described by Bast *et al.* in 1981 \(^1\)
- Topic of many studies to optimize the management of OC

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Variability in CA 125 and tumor size kinetics:
Background

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- Serum marker of epithelial ovarian cancers
- Described by Bast *et al.* in 1981
- Topic of many studies to optimize the management of OC

Variability in CA 125 and tumor size kinetics:

$\rightarrow$ **CA 125 kinetics modeling** to consider inter- and intra-individual variability
Objectives

1. Build a population K-PD semi-mechanistic model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy

2. Validate "externally" this model

3. Assess the prognosis value of CA 125 on tumor dynamics
Objectives

1. **Build** a population K-PD semi-mechanistic model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy.

2. **Validate** "externally" this model.
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3. **Assess** the *prognosis* value of CA 125 on tumor dynamics.
CALYPSO trial: 
- Randomized, multicenter, phase III non-inferiority study
- Platinum-sensitive ROC patients
- Carboplatin - Pegylated Liposomal Doxorubicin (CD) VS Carboplatin - Paclitaxel (CP)

Patients and Methods

Patients

- **CALYPSO trial**: Randomized, multicenter, phase III non-inferiority study
  - Platinum-sensitive ROC patients
  - Carboplatin - Pegylated Liposomal Doxorubicin (CD) VS Carboplatin - Paclitaxel (CP)

- **Data**:
  - 535 ROC patients
  - Baseline covariates: age, weight, lesion size...
  - 10 CA 125 concentrations and 4 tumor size values per patient
  - Modeling during 500 days
Data splitting

CALYPSO trial
N = 535
Patients and Methods

Methods

Data splitting

CALYPSO trial
N = 535

2/3 Randomization

Learning dataset
N = 357

Model building
Data splitting

CALYPSO trial
N = 535

Learning dataset
N = 357

Validation dataset
N = 178

Model building

Model evaluation

2/3 Randomization

1/3
Patients and Methods

Methods

Model building

- K-PD model
- Population analysis: Monolix 4.1.2
- Model internal evaluation:
  - goodness-of-fits plots
  - simulation-based diagnostics

- Model structure
- Parameters distributions
**Patients and Methods**

**Methods**

**Model building**
- K-PD model
- Population analysis: Monolix 4.1.2
- Model internal evaluation:
  - goodness-of-fits plots
  - simulation-based diagnostics

**Model evaluation**
- Tumor size and CA 125 predictions
- Evaluation metric: Normalised Prediction Distribution Errors (NPDE)

**Learning dataset**

**Validation dataset**

- Model structure
- Parameters distributions
Patients and Methods

K-PD semi-mechanistic model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy

Drug kinetics

Tumor dynamics

CA 125 kinetics
Patients and Methods

K-PD semi-mechanistic model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy

Drug kinetics

\( CP \) or \( CD \)

\[ \begin{align*}
\text{Q1: blood} & \quad K1 \\
\text{Q2: transit} & \quad K1
\end{align*} \]

Tumor dynamics

CA 125 kinetics
Patients and Methods
K-PD semi-mechanistic model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy

Drug kinetics

\(CP \ or \ CD\)

Tumor dynamics

\(K_{in_{TS}}\)

\(Q_{50}\)

\(K_{out_{TS}}\)

CA 125 kinetics
Patients and Methods
K-PD semi-mechanistic model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy.
Patients and Methods
K-PD semi-mechanistic model describing tumor size and CA 125 kinetics in ROC patients after chemotherapy
### Results

Typical parameters and inter-individual variability estimated

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Estimate</th>
<th>RSE estimate (%)</th>
<th>IIV (CV)</th>
<th>RSE IIV (%)</th>
<th>Shrinkage (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.054</td>
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<tr>
<td>$K_{IN_{TS}}$</td>
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<tr>
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<td>IU</td>
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<td>33</td>
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Covariates at baseline:

- Basal lesion size on $Kin_{TS}$: larger tumor growth for patients with a lesion size $> 5cm$
- Basal number of lesions on $Q_{50}$: treatment more potent in patients with only 1 lesion site
Results
Model internal evaluation: NPDE distribution

Tumor size

CA 125

Predictions

Predictions

Density

Density

NPDE

NPDE

Time

Time
Results
Model internal evaluation: Visual Predictive Check

Tumor size

- Observations percentiles
- Simulated confidence interval 90%
- Simulated c.i 50%
- Simulated c.i 10%

CA 125

Log (Tumor Size) vs Time (days)

Box Cox (CA 125) vs Time (days)
Results

Model internal evaluation

K-PD combined model of drug kinetics, tumor dynamics and CA 125 kinetics:

- Data satisfactorily described (GOFs, not shown)
- Adequate predictive performance (NPDEs, VPCs)

→ Model internal validation achieved
Results

Model "External" evaluation

**Method:**
- Model structure
- Parameters distributions
- Validation dataset

→ Tumor size and CA 125 predictions
Results
Model "External" evaluation

- **Method:**
  - Model structure
  - Parameters distributions
  - Validation dataset
  
  ➔ Tumor size and CA 125 predictions

- **NPDE:**

  ➔ Model "external" validation **achieved**
Results
Clinical applications: Treatment comparison

Carboplatin - Pegylated Liposomal Doxorubicin (CD) VS Carboplatin - Paclitaxel (CP):

EBEs not significantly different in both groups.
Results
Clinical applications: Treatment comparison

Carboplatin - Pegylated Liposomal Doxorubicin (CD) VS Carboplatin - Paclitaxel (CP):

EBEs not significantly different in both groups

→ In agreement with CALYPSO trial conclusions
Results

Clinical applications: Tumor size monitoring

- Observations
- Tumor size: 500 days
- CA 125: 500 days
Results

Clinical applications: Tumor size monitoring

- Observations
- Tumor sizes predictions

Tumor size: 500 days
CA 125: 500 days
Results

Clinical applications: Tumor size monitoring

Tumor size Predictions versus Observations

Unbiased (MPE = 2 %)
Limited precision (MAE = 48 %)
Results
Clinical applications: Tumor size monitoring

Tumor size Predictions versus Observations

Unbiased (MPE = 2 %)
Limited precision (MAE = 48 %)

→ Tumor size prediction from CA 125 at the population level (high values)
Results
Clinical applications: Tumor size forecast

- Tumor size
- CA 125

3rd cycle

Observations

500 days

500 days
Results

Clinical applications: Tumor size forecast

- Observations
- Tumor sizes predictions

Tumor size

CA 125

3rd cycle

500 days

500 days
Results

Clinical applications: Tumor size forecast

Tumor size Predictions versus Observations

Unbiased (MPE = 0.5 %)
Limited precision (MAE = 48 %)
Results
Clinical applications: Tumor size forecast

Tumor size Predictions versus Observations

Unbiased (MPE = 0.5 %)
Limited precision (MAE = 48 %)

→ Prognosis value of modeled CA 125 to early forecast tumor size at the population level
First combined model, internally and externally validated, characterizing tumor size and CA 125 kinetics in ROC patients, after chemotherapy.
First combined model, internally and externally validated, characterizing tumor size and CA 125 kinetics in ROC patients, after chemotherapy.

- Treatment or dosing regimen comparison
- Tumor size monitoring using CA 125 at the population level
- CA 125 is not a surrogate marker of measured lesion size at the individual level
Discussion

• Tumor size observations: sum of the longest dimension for all target lesions $\rightarrow$ May not take into account complete tumor burden and metastases in ROC patients
Discussion

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- CA 125 assumes to be produced by all tumor cells
Discussion

- Tumor size observations: sum of the longest dimension for all target lesions → May not take into account complete tumor burden and metastases in ROC patients
- CA 125 assumes to be produced by all tumor cells
- Predictive value of CA 125 kinetics on Progression Free Survival in a similar ROC patients population:

![Graph showing progression free survival over time]

Discussion

- Tumor size observations: sum of the longest dimension for all target lesions $\rightarrow$ May not take into account complete tumor burden and metastases in ROC patients

- CA 125 assumes to be produced by all tumor cells

- Predictive value of CA 125 kinetics on Progression Free Survival in a similar ROC patients population $^3$:

$\rightarrow$ Interest of CA 125 kinetics analysis to predict treatment success or failure
To confirm our results on other data in ROC
1. To confirm our results on other data in ROC

2. To apply population modeling approach on other biomarkers:
   - PSA in prostate cancer
   - hCG in gestational trophoblastic disease
   - ...


Thank you!
Backslide
CALYPSO trial
N = 974 enrolled patients

N = 661 patients with no missing data

N = 535 patients with data available for modeling analyses

Exclusions:
- 16 patients with time missing data
- 297 patients with tumor size missing data

Exclusions:
- 39 patients with CA-125 observations number < 4
- 35 patients with tumor size values number < 2
- 52 patients CA-125 constantly < 25 U/mL

Randomization

Learning dataset
N = 357

Validation dataset
N = 178
Data distribution of dependent variables tumor size and CA 125

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<th>Characteristics</th>
<th>Data</th>
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<tbody>
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<td>PFS 1st chimio (months)</td>
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<td>Patient Therapy Free Interval (months)</td>
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<td>Number of cycles</td>
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Box Cox transformation

\[ CA \, 125' \lambda = \frac{CA \, 125^\lambda - 1}{\lambda} \]

\[ \lambda = -0.16 \]
Model equations

\[
\begin{align*}
\frac{dQ_1}{dt} &= -K_1 \times Q_1 \\
\frac{dQ_2}{dt} &= K_1 \times Q_1 - K_1 \times Q_2 \\
\frac{dT_\text{S}}{dt} &= K_{\text{in}_{TS}} \times \left( 1 - \frac{Q_2}{Q_50 + Q_2} \right) - K_{\text{out}_{TS}} \times T_{\text{S}} \\
\frac{dC_\text{A}}{dt} &= K_{\text{in}_{CA}} \times \exp(K_2 \times VARTS) - K_{\text{out}_{CA}} \times C_{\text{A}}
\end{align*}
\]
Results
Model internal evaluation: Predictions versus Observations

Tumor size

CA 125
Individual Fits

- Example of tumor size individual fits for 3 ROC patients

![Graphs of tumor size over time for 3 patients](image)

- Example of CA 125 individual fits for 3 ROC patients

![Graphs of CA 125 over time for 3 patients](image)
Results

Predictions performances criteria

- Bias measure $\rightarrow$ Mean Prediction Error (MPE):

$$MPE = \frac{\sum_{i=1}^{N}(Predicted - Observed)}{N}$$

- Precision measure $\rightarrow$ Mean Absolute prediction Error (MAE):

$$MAE = \frac{\sum_{i=1}^{N}|Predicted - Observed|}{N}$$