MODELING OF CARDIAC BIOMARKERS IN BREAST CANCER PATIENTS TREATED WITH ANTHRACYCLINE AND TRASTUZUMAB REGIMENS

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Major findings

Sensitivity for left ventricular ejection fraction (LVEF) decline under trastuzumab treatment is explained by three cardiac biomarkers:

1. Maximum troponin T concentrations during anthracycline treatment
2. Baseline NT-proBNP concentrations
3. Baseline LVEF measurements

Background

- Trastuzumab is used to treat HER2-recepor positive breast cancer.
- Trastuzumab treatment is associated with cardiotoxicity, manifesting in a decline of LVEF values: the fraction of blood that is pumped out of the heart.
- Patients are often pretreated with anthracyclines, also known to induce cardiotoxicity, leading to myocyte damage which translates into an increase in troponin T concentrations.
- LVEF values are generally used to detect drug-induced cardiotoxicity, however troponin T and NT-proBNP concentrations have also been suggested to allow early detection of cardiotoxicity.

Objective

In this analysis we aim to quantify the kinetics and exposure-response relationship of troponin T, NT-proBNP and LVEF measurements, in patients receiving anthracycline and trastuzumab treatment.

Data

Data was obtained from a clinical trial investigating the effect of candesartan on trastuzumab induced cardiotoxicity, n=209 [1].
Available data included:

- Repeated measurements of troponin T, NT-proBNP and LVEF
- Individual dosing records of anthracycline and trastuzumab

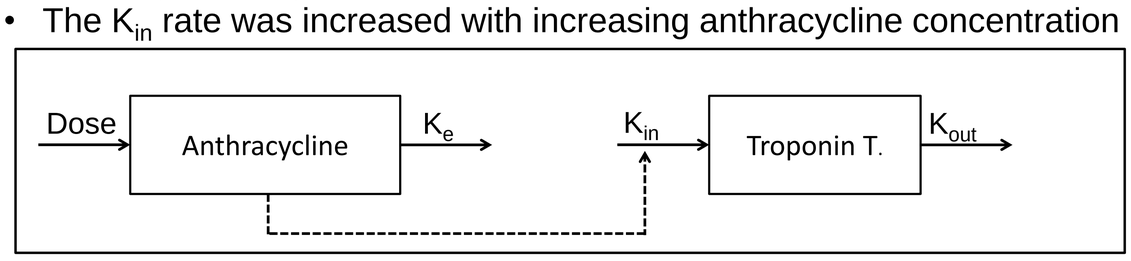
Methods

Pharmacokinetics

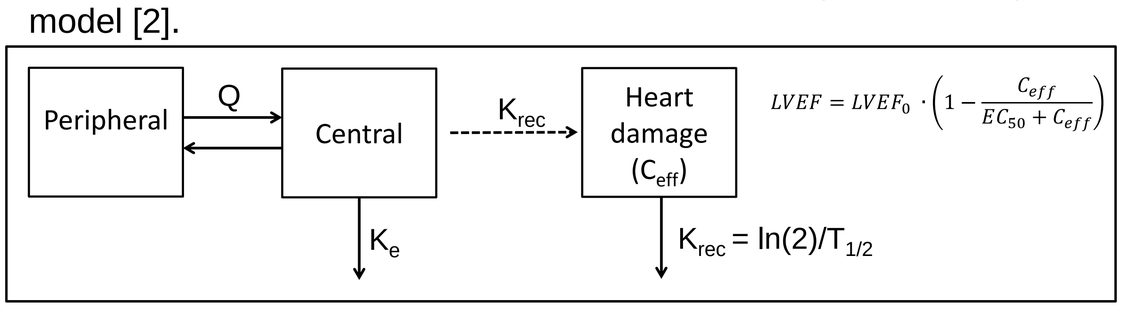
- Mean PK of trastuzumab was described using a published PK model. [3]
- A K-PD approach was used for anthracyclines (doxorubicin & epirubicin) [4].

Pharmacodynamics:

- Troponin T was best described by a turn-over model to associate anthracycline exposure to troponin T concentrations
- The K_{in} rate was increased with increasing anthracycline concentration



- An effect-compartment model was used to associate trastuzumab exposure to LVEF measurements.
- The effect-compartment resembles the heart damage and the damage is modeled to affect the baseline value of LVEF ($LVEF_0$) with an E_{max} model [2].



- For NT-proBNP only baseline values before start trastuzumab (BNP_0) were included by estimation of the observed concentrations.

Covariates

The following variables were tested as covariates:

- Radiotherapy: previous treatment, frequency and laterality
- Hypertension: diagnosis and state (active/dormant)
- Randomization to candesartan

Results

- Sensitivity for LVEF decline (EC_{50} parameter) was significantly affected by the maximum troponin T concentration ($CMAX_{trop}$) during anthracycline treatment, BNP_0 concentration and $LVEF_0$ value:

$$EC_{50} = TVEC_{50} \cdot \left(\frac{CMAX_{trop}}{14}\right)^{-1.04} \cdot \left(\frac{BNP_0}{62.1}\right)^{-0.418} \cdot \left(\frac{LVEF_0}{0.609}\right)^{7.54}$$

Table 1: EC_{50} : Sensitivity for different scenarios

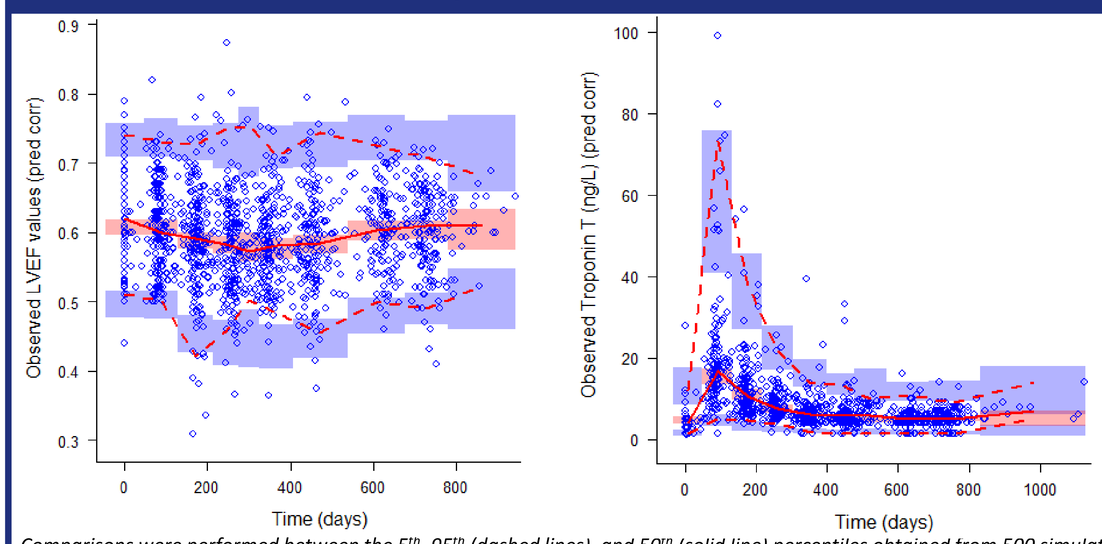
Scenario	EC_{50} (mg/L effect conc.)	Sensitivity
Population estimate	1700	-
$CMAX_{trop}$ of 20 ng/L	1173	Increased
BNP_0 of 150 pmol/L	1175	Increased
$LVEF_0$ of 0.55	788	Increased

Table 2: IIV on EC_{50}

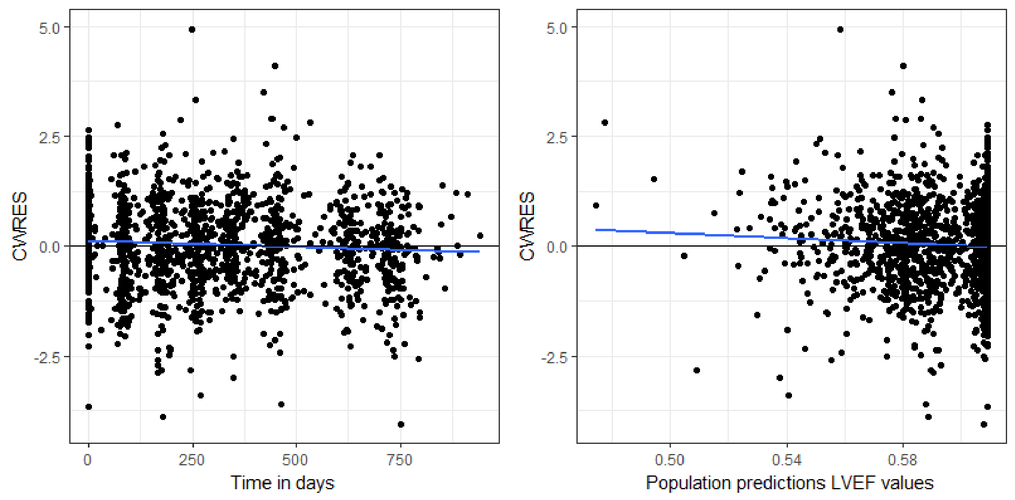
Scenario	% IIV (RSE (%))	dIIV
No biomarker effects	88.4 (9)	-
$CMAX_{trop}$	54.5 (15)	33.9%
$CMAX_{trop}$ + $LVEF_0$	25.5 (89)	29.0%
$CMAX_{trop}$ + $LVEF_0$ + BNP_0	21 (179)	4.5%

- The slope effect of anthracyclines on the K_{in} rate of troponin T was 2 times higher for doxorubicin compared to epirubicin.

VPCs for LVEF and troponin T



Comparisons were performed between the 5th, 95th (dashed lines), and 50th (solid line) percentiles obtained from 500 simulations and the observed LVEF values and troponin T concentrations (open circles).



CWRES vs. time and CWRES vs. population predictions for the model describing LVEF values over time.

Conclusions

- The $CMAX_{trop,}$ explained 34% of variability in sensitivity (EC_{50}) to LVEF decline, followed by $LVEF_0$ (29%) and BNP_0 (4.5%).
- The slope effect at which troponin T is increased by anthracycline treatment, was a 2-fold higher for doxorubicin compared to epirubicin.
- Evaluated covariates did not significantly influence the dynamics of cardiotoxicity represented in this model.
- The $CMAX_{trop}$ during anthracycline treatment and baseline values of NT-proBNP and LVEF can support prediction of patient sensitivity to LVEF decline during trastuzumab treatment.

References
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