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-receptor 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.

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 Kₘₚ 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 (LVEF₀) with an Emax model [2].

For NT-proBNP only baseline values before start trastuzumab (BNP₀) were included by estimation of the observed concentrations.

VPCs for LVEF and troponin T

Conclusions

- The CMAXₜrop explained 34% of variability in sensitivity (EC₅₀) to LVEF decline, followed by LVEF₀ (29%) and BNP₀ (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 CMAXₜrop during anthracycline treatment and baseline values of NT-proBNP and LVEF can support prediction of patient sensitivity to LVEF decline during trastuzumab treatment.

References