Poster

[P25-9] P25-9: Oncologic drugs (1)

Chair: Ryuji Ikeda, Japan

Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall)

[P25-9-6] New effective and sensitive method for quantification of tamoxifen, N-desmethyl tamoxifen, 4-hydroxy tamoxifen and endoxifen in human plasma

Gerd Ackehed[1], Anton Pohanka[2], Per Hall[3], Olof Beck[4] (1.Karolinska University Laboratory, 2.Karolinska University Laboratory, 3.Karolinska University Laboratory, 4.Karolinska University Laboratory)

Keywords: Tamoxifen, Endoxifen isomers, Validation

Background

The aim of the randomized controlled trial Karisma is to reduce the number of women affected by breast cancer. The anti-hormonal drug Tamoxifen, used since 40 years back in the adjuvant setting, has been shown to reduce the incidence of breast cancer with nearly 50% if administrated to healthy women but is not used because of severe side effects. In the Karisma trial women at high risk of breast cancer are randomized to five different doses of Tamoxifen or placebo. For some patients the treatment of Tamoxifen is not as effective as for the majority. The metabolism and formation of active metabolites and especially (Z)-N-desmethyl-4-hydroxy Tamoxifen (Z-Endoxifen) has been subject to attention due to its affinity to the estrogen receptor. To be able to follow the metabolite formation also in low dose treatments a sensitive bioanalytical method for determination of Tamoxifen (TAM) and its metabolites N-desmethyl-tamoxifen (N-DM-TAM), (Z)-4-hydroxy Tamoxifen (4-OH-TAM), and (Z)-endoxifen in human plasma was developed.

Methods

The sample preparation of human EDTA-plasma is based on protein precipitation followed by determination with LC-MS/MS (Dionex Ultimate 3000 and TSQ Quantiva, Thermo Scientific). The method uses stable isotopically labeled internal standards for all quantified analytes.

Results

The method utilizing a 200 uL sample aliquot, has a calibration range of 0.0500-50.0 ng/mL for (Z)- and (E)-endoxifen, 0.100-100 ng/mL for 4-OH-TAM and 1.00-1000 ng/mL for N-DM-TAM and tamoxifen. At the validation of the analytical method the calibration ranges were tested at 8 concentration levels (in singlicate) with quality-control samples at 4 concentration levels (6 replicate of each). The within- and between-batch accuracy and precision measurements were determined by analysis in three separate analytical runs. The validation fulfils the criteria according to the European Medicines Agency guideline on bioanalytical method validation.

Conclusions

A method has been successfully validated for the determination of (Z)-endoxifen, (E)-endoxifen, (Z)-4-OH-TAM, N-DM-TAM and tamoxifen in human plasma. The method was validated in the range 0.0500-50.0 ng/mL for (Z)- and (E)-endoxifen, 0.100-100 ng/mL for 4-OH-TAM and 1.00-1000 ng/mL for N-DM-TAM and tamoxifen. The lower limit of quantification was set at the lowest calibration concentration for each analyte.