
Oral

[O25-6] O25-6: Drug assay

Chairs: Hiroaki Yamaguchi, Japan / Hiromi Shibasaki-Hirano, Japan

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[O25-6-1] Simultaneous determination of imatinib, sunitinib, erlotinib and metabolites in human plasma by LC-MS/MS

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Background

Therapeutic drug monitoring (TDM) is not often applied in oncology, although some of the new oral targeted therapies, for example tyrosine kinase inhibitors (TKIs), have been shown to be suitable candidates.

Concentration–effect relationships are defined for imatinib, sunitinib, and erlotinib, which make the TDM of these TKIs feasible in routine clinical practice settings. Both imatinib and sunitinib have active metabolites, which also are of interest for determination.

Methods

A LC-MS/MS method was developed for the determination of imatinib, N-desmethyl-imatinib, sunitinib, N-desethyl-sunitinib and erlotinib in human plasma using a Waters Acquity LC-system coupled to a Waters Quattro Premiere XE mass spectrometer, operating in positive mode with electrospray ionization. The analytes were separated on an Acquity UPLC BEH C18 2.1 x 50 mm 1.7 m column (Waters) using a gradient with 10 mM ammonium formate and methanol with a total chromatographic time of 2.5 minutes. The samples were deproteinized with methanol containing deuterated internal standards for all five analytes followed by direct injection of the supernatant on to the LC-MS/MS.

Results

The method was fully validated in the range 100-10000 ng/mL (imatinib and N-desmethyl-imatinib), 10-1000 ng/mL (sunitinib and N-desethyl-sunitinib) and 50-10000 ng/mL (erlotinib) according to the European Medicines Agency's (EMA) guideline on bioanalytical method validation. Accuracy (<±15%) and coefficients of variation for precision (<15%) were within EMA criteria for all analytes at all quality control levels. No significant difference was found between citrate, heparin and EDTA plasma and serum regarding quantitative and qualitative matrix effects and process efficiency. The method was adapted for routine analysis of patient samples.

Conclusions

A rapid and easy to perform method for simultaneously determination of imatinib, N-desmethyl-imatinib, sunitinib, N-desethyl-sunitinib and erlotinib was developed and fully validated according to EMA guidelines. All acceptance criteria for the validation were fulfilled. The method has been adapted for routine analysis with positive results and is now in use at the Karolinska University Hospital TDM laboratory. Utilizing TDM for TKIs will assist rational and robust dose optimization, permit individualized therapy, and help to optimize the usage of these agents.