Symposium

[S-16] S-16: TDM of 5-FU

Chairs: Edward Chu, USA / Yasutsuna Sasaki, Japan
Wed. Sep 27, 2017 10:30 AM - 12:00 PM Room D (1F)

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[S-16-3] Therapeutic drug monitoring of 5-fluorouracil by LC-MS/MS

Anna Hansson[1], Louise Gustafsson[2], Yuko Ronquist-Nii[3], Alan Fotoohi[4], Anton Pohanka[5] (1.Karolinska University Laboratory, Clinical Pharmacology, Stockholm, Sweden, 2.Karolinska University Laboratory, 3.Karolinska University Laboratory, 4.Karolinska University Laboratory, 5.Karolinska University Laboratory)
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Background

There is growing evidence showing that dosing based on the concentration of 5-fluorouracil (5-FU) in plasma can improve efficacy and reduce toxicities of 5-FU-based treatment. Dihydropyrimidine dehydrogenase (DPD) has an important role in the metabolism of 5-FU and a deficiency in that enzyme can cause a toxic effect of the drug. This is why screening for DPD deficiency and therapeutic drug monitoring (TDM) of 5-FU in plasma can help to optimize treatment.
As 5-FU in whole blood is rapidly degraded by DPD, the plasma needs to be separated shortly after sampling, or a DPD inhibitor such as gimeracil can be added to the blood tube. At present Karolinska University Hospital TDM laboratory determines 5-FU concentrations by immunoassay (My5-FU, Saladax) but now expands through a LC-MS/MS method with possibility to detect gimeracil.

Methods

A LC-MS/MS method for quantifying 5-FU in plasma and the presence of the DPD inhibitor, gimeracil was developed and validated. The analytical instrument used consisted of a Dionex UltiMate 3000 with a Thermo Scientific TSQ Quantiva mass spectrometer operated in both positive and negative electrospray ionization mode. Sample preparation was by protein precipitation, by adding methanol containing isotopic labeled internal standard, evaporated to dryness and reconstituted with 0.1% formic acid in water. Retention was sufficient on a Hypersil Gold C8 50×2.1 mm, 1.9 m column (Thermo Scientific).

Results

The method was validated according to the European Medicines Agency’ s guidelines and fulfilled all criteria for accuracy and precision, stability, robustness and both qualitative and quantitative matrix effects within the quantification range 0.1-20 g/mL. Method comparison versus immunoassay for patient samples (n=14) containing 5-FU was satisfactory showing an expected lower concentration for the LC-MS/MS method.

Conclusions

The developed method can improve the treatment for patients with colorectal cancer by adjusting the dose between infusion sessions from 5-FU concentrations in plasma. The ability to monitor gimeracil also makes it possible to verify preanalytical stabilisation of DPD and avoid underestimation of 5-FU exposure and incorrect dose increment recommendation. To improve the treatment further a phenotyping method for DPD is being developed.