Oral

[O25-6] O25-6: Drug assay

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[O25-6-2] Simultaneous quantification of busulfan, clofarabine and F-ARA-A using isotope labelled standards and standard addition in plasma by LC-MS/MS for exposure monitoring in hematopoietic cell transplantation conditioning

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Background

In allogeneic hematopoietic cell transplantation (HCT) it has been shown that over- or underexposure to conditioning agents have an impact on patient outcomes. Conditioning regimens combining busulfan (Bu) and fludarabine (F-ARA-A) with or without clofarabine (Clo) are gaining interest worldwide in HCT. A simultaneous analysis of Bu, Clo and F-ARA-A in one analytical run would be of great interest to determine the optimal exposure for HCT. Furthermore, for the bioanalysis of drugs it is common to use stable isotope labelled standards (SILS). However, when SILS are unavailable (in case of Clo and F-ARA-A) or very expensive, standard addition may serve as an alternative to correct for recovery and matrix effects.

Methods

A fast analytical method, including standard addition methodology for the quantification of . After protein precipitation, Bu, Clo and F-ARA-A were simultaneous analyzed with liquid chromatography-tandem mass spectrometry (LC-MS/MS), Validation was performed in accordance with European Medicines Agency guidelines.

Results

The assay proved linear (R2>0.995) between 10-10000 g/L for Bu and 1-5000 g/L for Clo and F-ARA-A. The lower limits of quantification (LLOQ) were for Bu 10 g/L and for Clo and F-ARA-A 1 g/L, respectively. Variation coefficients of LLOQ were within 20% and for low medium and high controls were all within 15%. Comparison of Bu, Clo and F-ARA-A standard addition results correspond with those obtained with calibration standards in calf serum. In addition for Bu, results obtained by this study were compared with historical data analysed within TDM.

Conclusions

A rapid method for the simultaneous quantification of Bu, Clo and F-ARA-A in plasma was developed. In addition, a robust and cost-effective method to correct for matrix interference by standard addition was established.