Oral

[O27-3] O27-3: Oncology (1)

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[O27-3-3] Towards in-silico-guided within-cycle adjustment of high-dose methotrexate in patients with lymphoid malignancies

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Background

High-dose methotrexate (HD-MTX) is a highly effective anticancer treatment. Clinical trials have suggested targeting $AUC_{0\text{-}Inf}$ which correlated best with favourable clinical outcome. The objective of the present study was to develop an in-silico guided dosing algorithm for within-cycle adjustment of high-dose methotrexate in patients with lymphoid malignancy.

Methods

The predictive performance (within-, across-cycle) of 4 published MTX population PK models was evaluated on 12 patients with lymphoid malignancy contributing 397 MTX samples over up to 8 dosing occasions. The best model was used in conjunction with D-optimal design to (i) determine the within-cycle sampling time point of highest accuracy and precision in AUC determination and (ii) derive the target AUC range (40^{th} to 60^{th} percentile of the AUC distribution obtained from the conventional dose 5 g/m^2 if <46 years, 3 g/m^2 if 46 years administered as a 24 h infusion). A dosing algorithm for AUC-targeted adjustment of the infusion rate was programmed in the ‘R’ software and compared to conventional dosing by clinical trial simulations.

Results

The population PK model by Joerger et al. 2011 provided the best predictive performance. Sampling at 8 h provided unbiased estimation of the AUC at a relative RMSE of 22.2 %. Hence, the infusion rate could be individualised at 10 h to allow 2 h for analysis and interpretation of the PK samples. For the conventional dosing algorithm, AUC was highly variable ($PI_{10\text{-}90}$: 823-2613 mol/L·h) and only 18.1% were in the target range. For the in silico-guided dosing algorithm, AUC was less variable ($PI_{10\text{-}90}$: 1062-2054 mol/L·h) and 30.2% of the patients were in the target range already at the first occasion. A sample during 54-72 h from the previous occasion further reduced the AUC spread to 1165-1882 mol/L·h and put 40.9% in the target range. The rate of sustained high MTX concentrations (>0.5 mol/L at 54 h) was reduced from 37.6% to 30.8% using the in silico-guided algorithm.

Conclusions

The algorithm will be clinically evaluated and precise target values may be refined. Subsequently, it will be implemented into the open-access TDMx-software to foster in-silico-guided dosing in high-dose MTX treatment.