Development of an adaptive dosing approach for doxorubicin in paediatric cancer patients

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Background

Anthracyclines, such as doxorubicin, are known for causing potentially irreversible cardiotoxicity. The prevention of long-term cardiac side effects is of particular importance in childhood cancer survivors. The reduction of variability in systemic therapy intensity (drug exposure and peak concentrations) holds promise to improve the safety of doxorubicin application. In view of the large heterogeneity in current dosing strategies, standardised dosing algorithms that reflect individual differences in pharmacokinetics (PK) are needed. Both (i) *a priori* dose adaptations that take into account relevant covariates and (ii) adaptive drug administration based on a single or few drug levels and subsequent Bayesian estimation of individual PK parameters could be considered for reducing variability.

Methods & Results

Evaluation of a standardised *a priori* dose adaptation

The effect of a dosing formula derived from a published popPK model for doxorubicin in children (described in [1]) on variability in drug exposure (AUC) was evaluated based on data from the EPOC-MS-001-Doxo ('EPOC') trial (clinicaltrials.gov identifier: NCT01095926). The proposed dosing formula takes into account individual BSA and age. The model-predicted AUC of an 18-year-old boy with median demographics served as target for dose calculation.

- Calculation of adjusted doxorubicin doses for 94 patients from the EPOC trial (formulas 1 – 2)

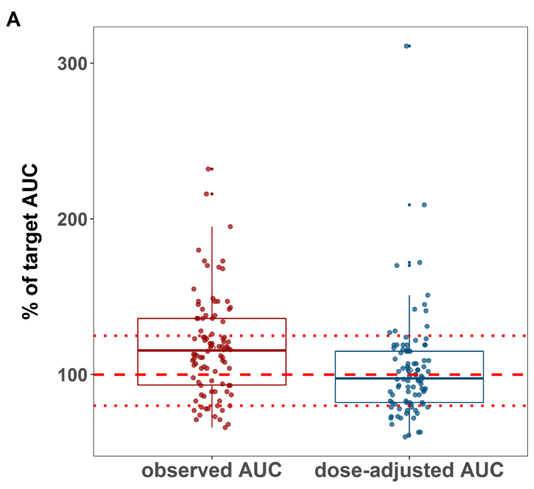
  (1) $Cl_{model\text{-}predicted} = 9.26 * (1 + (BSA - 0.77) * 1.30) * (1 + (AGE/5.32)^{**}0.286)$

  (2) $Dose_{adjusted} = Dose_{18\ years} * Cl_{model\text{-}predicted}/CL_{18\ years}$

- Calculation of observed and dose-adjusted AUC values using the empirical Bayesian clearance estimates (CL_{EPOC}) derived from the EPOC data (formula 3)

  (3) $AUC = Dose/CL_{EPOC}$

- Normalisation of observed and dose-adjusted AUC values to the target AUC and calculation of bias, precision and the probability to attain a target range of 80 – 125 %



(A) Observed AUC from 94 patients from the EPOC trial and dose-adjusted AUC relative to the target AUC of a typical 18-year-old boy. The dashed red line indicates the target AUC of 100 %, dotted red lines indicate a range of 80-125 %.

- Only **small decrease in precision** from 21 % (95 % CI 18 – 23 %) to 17 % (95 % CI 13 – 19 %)
- Percentage of AUC attaining the target range **58.5 %** for observed and **69.1 %** for dose-adjusted AUC

Predictive performance of the PK model

The predictive power of the population PK model in a reduced sampling situation was investigated.

- Selection of patients from EPOC dataset with full PK profile (8 samples from 2 occasions) (= reference dataset)
- Generation of truncated datasets with 1 – 3 samples based on the reference dataset
- Computation of empirical Bayesian CL estimates based on the truncated datasets and the reference dataset (POSTHOC option with MAXEVAL = 0)
- Calculation of bias, precision and percentage of CL values within 10 % and 20 % error range

Table 1: Predictive power of the PK model based on a reduced number of samples

Scenario	Sample(s) retained (from occasion 1)	% CL within 10 % error range	% CL within 20 % error range	Bias [%] (95 % CI)	Precision [%] (95 % CI)
1	none	31.7	65.9	-2.6 (-17.1, 5.1)	18.9 (12.8, 21.3)
2	2	53.7	75.6	-2.8 (-7.2, 2.6)	7.8 (6.0, 15.2)
3	4	53.7	78.0	-3.5 (-9.0, 5.3)	9.2 (7.5, 16.8)
4	2,3	56.1	82.9	-3.5 (-6.5, 3.4)	8.5 (5.2, 13.0)
5	2,4	63.4	85.4	-0.8 (-5.9, 3.4)	7.5 (4.1, 12.3)
6	1,2,5	65.9	90.2	0.7 (-6.4, 5.7)	8.1 (6.3, 10.4)
7	1,3,5	68.3	90.2	-1.6 (-8.2, 4.2)	8.2 (5.7, 9.9)

Optimisation of the sampling design

The most informative sampling time points for a limited sampling design were identified based on Ds-optimality criteria using the R-script version of the optimal design software PopED [2]. Prior information was obtained from the PK model for DOX (see [1]). Optimisation was performed based on patient characteristics of the EPOC cohort as these were considered to represent typical paediatric cancer patients.

- 1 – 3 point sampling designs were separately investigated for patients subgroups (defined by dose and infusion time)
- Sampling space was constrained regarding practicability (no sampling within infusion or at night)
- To reduce calculation time only discrete time points (hourly) were investigated

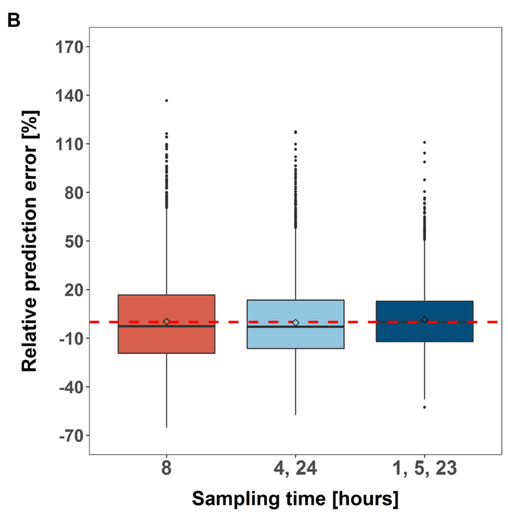
Table 2: Optimal design results for a doxorubicin limited sampling design

Group	Number of Samples	Dose [mg/m²]	Infusion time [h]	Optimised Sampling [h after start of infusion]
G1 (26 patients)	1	30	1	8
	2	30	1	4; 24
	3	30	1	1; 5; 23
G2 (26 patients)	1	20	4	8
	2	20	4	8; 23
	3	20	4	8; 21; 23
G3 (11 patients)	1	30	4	8
	2	30	4	4; 22
	3	30	4	4; 19; 22
G4 (12 patients)	1	50	6	6
	2	50	6	6; 19
	3	50	6	6; 19; 26

Predictive performance of optimal sampling designs

Exemplarily, the predictive performance of the optimal sampling designs for a treatment regimen with a 1 h infusion and a dose of 30 mg/m² (group 1, corresponding to the AIEOP-BFM ALL 2017 protocol) was investigated.

- Simulation of a complete dataset based on demographic data from ALL, Ewing sarcoma and Wilms tumour patients (n = 5442)
- Simulated individual CL values = ‚true' CL values
- Truncation of the dataset to include only the sampling times for the optimal 1/2/3 sampling design
- Bayesian estimation of individual CL values for each truncated dataset and comparison with simulated 'true' CL values



(B) Relative prediction error of CL values estimated based on the optimal sampling designs for group 1 compared to the simulated CL values. The dashed red line indicates a relative prediction error of 0 %.

- **Accurate prediction** of individual CL with bias ranging from **-2.9 %** (95 % CI -3.8 – -2.1 %) to **0.0 %** (95 % CI -0.6 – 0.5 %)
- **Moderate precision** ranging from **18.0 %** (95 % CI 17.4 – 18.6 %) to **12.5 %** (95 % CI 12.1 – 12.8 %)

Conclusion

- A small reduction in variability of drug exposure can be expected with *a priori* dose adaptations, though requires clinical validation
- Bayesian forecasting suggests that individual clearance can be accurately and precisely predicted based on a limited number of samples
- Adaptive doxorubicin dosing based on the most informative reduced sampling strategy might provide a further approach to better control variability

References

[1] Völler S, Boos J, Krischke M, Würthwein G, Kontny NE, Boddy AV, Hempel G. Age-Dependent Pharmacokinetics of Doxorubicin in Children with Cancer. Clin Pharmacokinet 2015; 54:1139–49
[2] Nyberg J, Ueckert S, Strömberg EA, Hennig S, Karlsson MO, Hooker AC. PopED: an extended, parallelized, nonlinear mixed effects models optimal design tool. Comput Methods Programs Biomed 2012; 108(2):789–805