Consensus on doxorubicin dosing in infants and children: pharmacokinetic simulations and Delphi process

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Background

Despite their cumulative dose-dependent cardiotoxicity anthracyclines, such as doxorubicin, are still a mainstay for the treatment of both adult and paediatric cancer. However, large differences exist in doxorubicin dose and infusion time between paediatric treatment protocols. Further, dose reduction strategies for infants vary largely between current protocols (table 1). As the prevention of chronic cardiac side effects receives more attention with the growing number of childhood cancer survivors, we ask how population pharmacokinetic (PK) simulations in combination with a Delphi approach could aid in developing more rational dosing strategies for doxorubicin in paediatric patients.

Table 1: Overview on a selection of current protocols for the treatment of paediatric cancers

Protocol	Dose and infusion time	Dose modification	
AIEOP-BFM ALL 2009	30 mg/m², 1 h, weekly (4x)	< 6 months:	67 % of BSA dose
		6 - 12 months:	75 % of BSA dose
		≥ 12 months:	100 % of BSA dose
SIOP 2001/GPOH	50 mg/m², 6 h	< 6 months:	50 % of BSA dose
		≥ 6 months or < 12 kg:	67 % of BSA dose
		≥ 6 months and ≥ 12 kg:	100 % of BSA dose
CWS-2002/ CWSSoTiSaR	2 x 20 mg/m², 3 h, day 1 + 2 (every 8 - 12 h)	< 6 months:	67 % of body-weight-based dose
		≥ 6 months or ≤ 10 kg:	100 % of body-weight-based dose (0.67 mg/kg)
		≥ 12 months and > 10 kg:	100 % of BSA dose
NB 2004 N4/N6	15 mg/m², 0.5 h, day 1 + 3 + 5 (N4) 30 mg/m², 4 h, day 6 + 7 (N6)	< 12 months:	100 % of body-weight-based dose
		≥ 12 months and < 10 kg:	100 % of body-weight-based dose (0.5 mg/kg (N4); 1.0 mg/kg (N6))
		≥ 12 months and ≥ 10 kg:	100 % of BSA dose
HR-NBL-1.7/ SIOPEN	45 mg/m², 48 h	≤ 5 kg:	67 % of body-weight-based dose
		> 5kg and < 12 kg:	100 % of body-weight-based dose (0.75 mg/kg/day)
		≥ 12 kg:	100 % of BSA dose

Methods & Results

Differences in therapy intensity (quantified as AUC and peak levels) were visualized for a selection of current protocols using Monte Carlo simulations. Simulations were performed based on a published population PK model (described in [1]) using NONMEM version 7.3. According to the model doxorubicin clearance is influenced by age and body surface area (formula 1).

$$CL = 9.26 * (1 + (BSA - 0.77) *1.30) * (1 + (AGE/5.32)**0.286) \qquad (1)$$

Representative simulation results were used as background information in a 3-round Delphi approach. The aim of the Delphi approach was to:

i. clarify the goals of dose adjustments and develop a consensus on a rational novel dosing concept for young children

ii. identify potential common PK targets between different protocols

Subsequently, a dosing rule that allows achieving the consented therapy intensity goals was developed using a simulation approach.

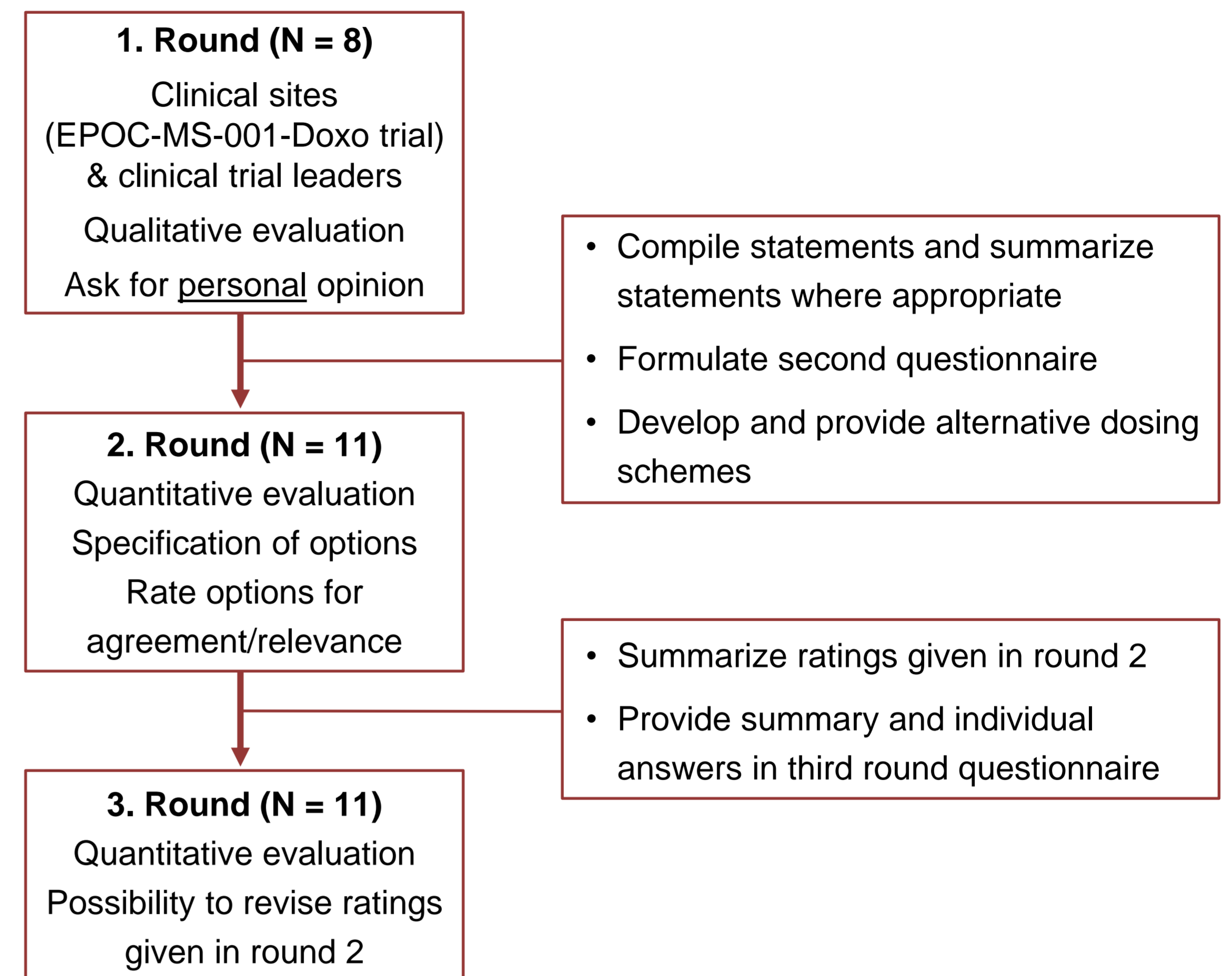### Differences in therapy intensity within/between protocols
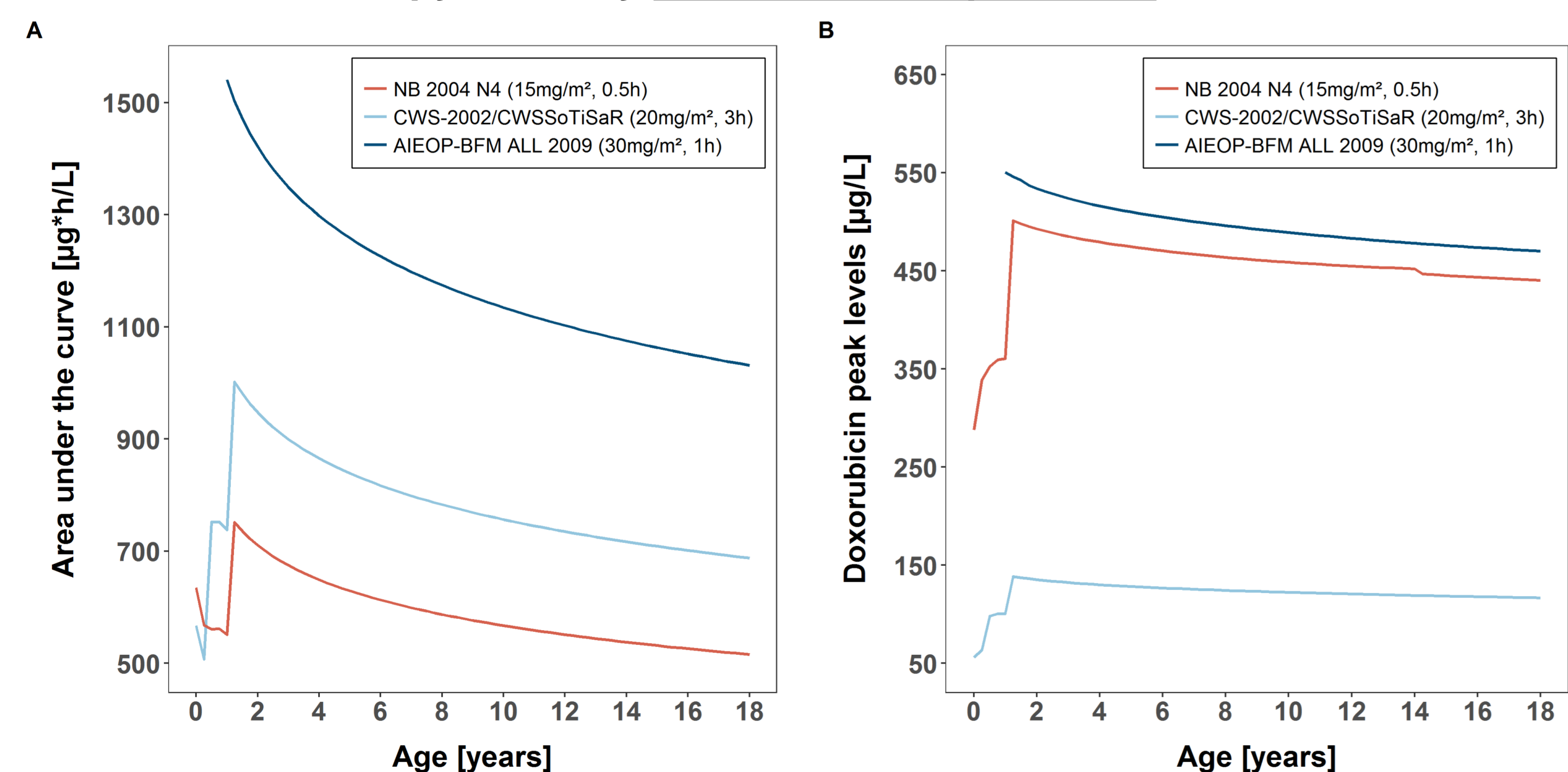
Median simulated doxorubicin (A) AUC and (B) peak levels for three selected paediatric protocols. For simulations generic children aged 0 – 18 years with median body height and weight were dosed according to the respective protocol (see table 1 for details). For the AIEOP-BFM ALL 2009 protocol only children ≥ 1 year were simulated according to the inclusion criteria of the study.

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. Clinical Pharmacokinetics 2015; 54:1139–49

Delphi approach to establish a consensus on doxorubicin administration

1. Round (N = 8)
Clinical sites
(EPOC-MS-001-Doxo trial)
& clinical trial leaders
Qualitative evaluation
Ask for personal opinion

- Compile statements and summarize statements where appropriate
- Formulate second questionnaire
- Develop and provide alternative dosing schemes

2. Round (N = 11)
Quantitative evaluation
Specification of options
Rate options for agreement/relevance

- Summarize ratings given in round 2
- Provide summary and individual answers in third round questionnaire

3. Round (N = 11)
Quantitative evaluation
Possibility to revise ratings given in round 2

➢ **Consensus on the goals of dose adjustments in young children:**
 – a priori dose adjustment to age and body surface area to achieve uniform AUC across age
 – prevention of high peak levels in very young children by prolonged infusion

➢ **Consensus on common PK targets:**
 – definition of target ranges for AUC, peak levels and time over threshold to guide doxorubicin administration
 – establishment of common PK targets between different protocols

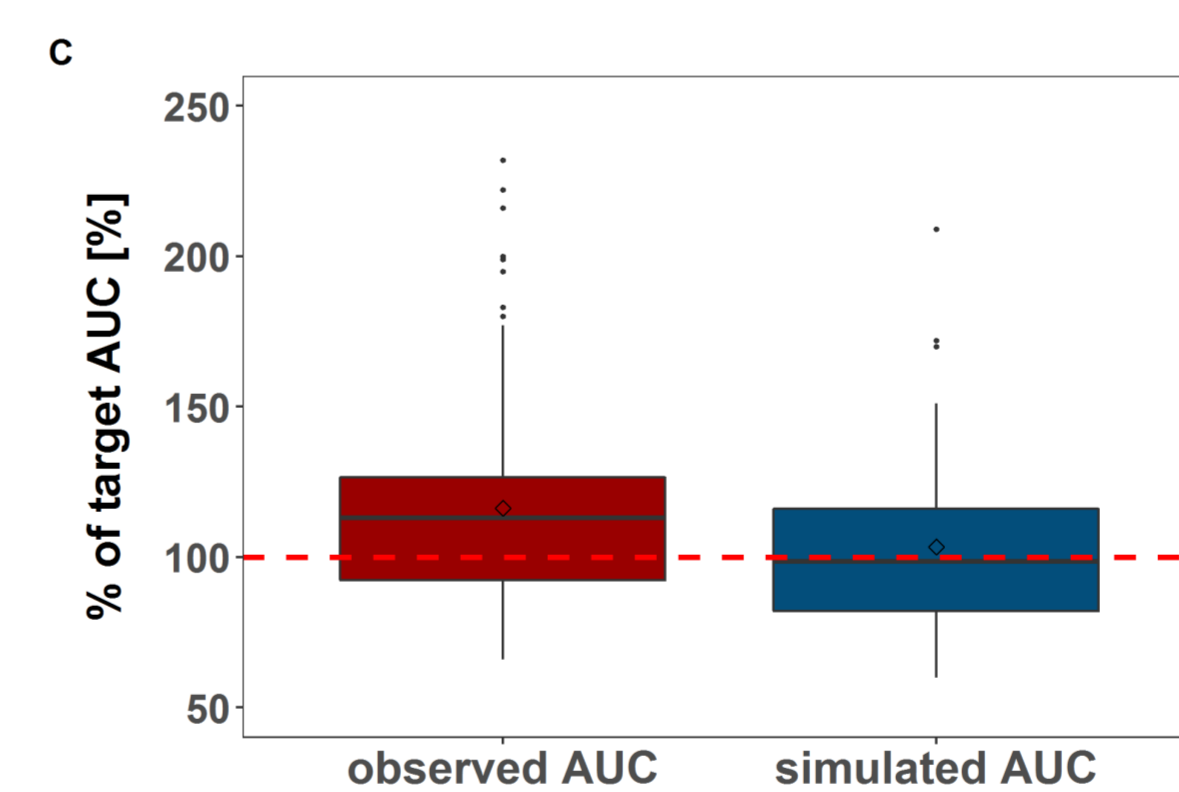### Development of a dosing rule for young children

I. Dose adjustment to achieve uniform AUC across age

- the AUC of a ´standard´ 18-year-old boy was considered as target AUC

thus $\quad AUC_{ind} = AUC_{18} \qquad (2)$

and $\quad Dose_{ind} = Dose_{18} * CL_{ind}/CL_{18} \qquad (3)$

 – CL_{ind} calculated according to formula 1
 – $Dose_{18}/CL_{18}$ refer to dose and CL of the 18-year-old reference patient

(C) Observed AUC from 88 patients from the EPOC-MS-001-Doxo trial and dose-adjusted AUC (calculated according to formula 3) relative to the target AUC of a median 18-year-old boy. AUC values are based on the post-hoc CL estimates taken from the NONMEM analysis [1]. The dashed red line indicates the target AUC of 100 %.

II. Prevention of high peak levels in very young children

- Assumption of dose adjustment according to formula 3

Table 2: Effect of a prolonged infusion on peak levels relative to the 18-year-old reference patient

	Doxorubicin peak levels relative to 18-year-old boy [%]					
Age [years]	Infusion time	Prolongation to		Infusion time	Prolongation to	
	0.5 h	0.75 h (x 1.5)	1 h (x 2)	2 h	3 h (x 1.5)	4 h (x 2)
0	53	38	30	57	41	32
0.5	73	52	40	76	54	42
1	77	54	42	79	56	44
1.5	79	56	43	82	58	45
2	81	57	44	83	59	46
18	100	-	-	100	-	-

Conclusion

Adjusting the doxorubicin dose to achieve defined therapy intensity goals in infants and young children may help to reduce the risk of chronic cardiac side effects while maintaining tumour efficacy. A simulation process in combination with a Delphi approach was conducted to establish a consensus for doxorubicin dosing rules in paediatric patients. Consented dosing rules need to be prospectively validated in a clinical trial.