Can we optimise doxorubicin treatment regimens for children with cancer? Pharmacokinetic simulations and a Delphi consensus procedure

CURRENT STATUS: UNDER REVIEW

BMC Pharmacology and Toxicology

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DOI:
10.21203/rs.2.13120/v1

SUBJECT AREAS
Toxicology Clinical Pharmacology

KEYWORDS
doxorubicin, children, cardiotoxicity, pharmacokinetics, Delphi procedure
Abstract

Background

Despite its cardiotoxicity doxorubicin is widely used for the treatment of paediatric malignancies. Current treatment regimens appear to be suboptimal as treatment strategies vary and do not follow a clear pharmacological rationale. Standardisation of dosing strategies in particular for infants and younger children is required but is hampered by scarcely defined exposure-response relationships. The aim is to provide a rational dosing concept allowing for a reduction of variability in systemic therapy intensity and subsequently unforeseen side effects.

Methods

Doxorubicin plasma concentrations in paediatric cancer patients were simulated for different treatment schedules using a population pharmacokinetic model which considers age-dependent differences in doxorubicin clearance. Overall drug exposure and peak concentrations were assessed. Simulation results were used to support a three round Delphi consensus procedure with the aim to clarify the pharmacological goals of doxorubicin dosing. A group of 28 experts representing paediatric trial groups and clinical centres were invited to participate in this process.

Results

Pharmacokinetic simulations illustrated the substantial differences in therapy intensity associated with current dosing strategies. The Delphi panel members recognised the clinical relevance of variability in therapy intensity and the need for optimisation of treatment regimens. Consensus among the panel members was obtained on a standardised a priori dose adaptation that individualises doxorubicin doses based on age and body surface area targeting uniform drug exposure.

Conclusions

A Delphi consensus procedure informed by pharmacokinetic simulations was successfully applied to specify the pharmacological goals of doxorubicin dose adaptations in children with cancer and to formulate a consistent dosing concept potentially improving the safety of doxorubicin administration.

Background
Since their introduction to chemotherapy in the 1960s anthracyclines have gained widespread use in the treatment of solid and haematological malignancies. Today, roughly 60 % of children with cancer receive anthracyclines, most commonly doxorubicin (DOX). Anthracyclines significantly increase event-free survival in Ewing’s sarcoma and a better antitumor efficacy is suggested for acute lymphoblastic leukaemia (ALL) [1]. However, a well-known drawback of this class of cytostatics is the induction of progressive chronic cardiotoxicity which is associated with cardiomyopathy, congestive heart failure and elevated mortality [2]. At a median of 6.4 years following treatment, subclinical cardiac damage has been reported in up to 57 % of cases [3] and 0.9 to 4.8 years after treatment an incidence of up to 16 % has been reported for clinical congestive heart failure [4]. Cumulative lifetime anthracycline dose has been early acknowledged as a major risk factor for chronic cardiac disease. This has led to restrictions of the total anthracycline dose in adults to 450 - 550 mg·m⁻² [5–7]. As the prevention of late cardiac events is of particular importance in paediatric cancer survivors with an otherwise long life expectancy, substantially lower total doses have been recommended for this group [7, 8]. However, with respect to cardiotoxicity there simply appears to be no safe anthracycline dose placing oncologists at a dilemma when assessing the risk-benefit ratio of anthracycline chemotherapy [9].

Given the fact of potentially fatal anthracycline-induced cardiomyopathy much attention has been paid to measures seeking to prevent adverse cardiac effects. Administration of weekly split-doses rather than one large dose as well as prolonged continuous infusions were among the most studied strategies. Essentially, these approaches rely on the assumption that drug exposure (expressed as area under the concentration-time curve (AUC)) is the most important determinant of antitumor efficacy and that reduced peak concentrations ($c_{\text{max}}$) as achieved with such schedules mitigate the toxic cardiac effect of anthracyclines without affecting their antitumor activity [10]. After 50 years of clinical use a plethora of studies in adult patients have been performed supporting the rationale of prolonged continuous infusion or split-dose schedules to reduce cardiotoxicity [10–12]. Of note, the duration of follow-up was rather small for most of the studies and thus reliable conclusions can largely
be drawn for early-onset cardiotoxic alterations. In paediatrics however, the fundamental goal must be the prevention of long-term rather than early-onset cardiac abnormalities which requires sufficiently long follow-up periods. In one of the rare prospectively designed randomized trials in children, 36 high- and standard-risk ALL patients received daunorubicin (DNR) either as bolus or as continuous infusion over 48 h and cardiac function was monitored over a median follow-up of 54 months. In this study, less cardiotoxicity was observed with continuous infusion compared to bolus (decline in cardiac function in 0/18 patients given DNR infusion and 4/18 patients given DNR bolus; \( p = 0.10 \)). The reduction of leukemic cell numbers was more rapid with the less cardiotoxic infusion compared to DNR bolus [13]. In contrast, Escherich et al. reported no difference in the decline of leukemic blasts 7 days after DNR infusion in a randomized comparison of 101 paediatric ALL patients receiving DNR either as 1 h or as 24 h infusion [14]. Unfortunately, the duration of follow-up in this trial was only 7 days. Thus, no conclusions on long term cardiac outcomes may be drawn. Results from a randomized trial with the hitherto longest follow-up were published by Lipshultz and colleagues. Echocardiographic data from 92 paediatric high-risk ALL patients, receiving DOX either as bolus (within 15 min) or as 48 h continuous infusion, were evaluated in this study. At a median follow-up of 8 years (range 3 - 13 years) the authors were unable to find a significant difference in cardiac structure or function between the two treatment groups, concluding that compared to bolus continuous DOX infusion does not provide improved long term cardioprotection in this patient population [15, 16]. Does continuous infusion and thus lower plasma concentration affect the tumour response? Again, for the paediatric situation this question cannot be answered conclusively. At least some evidence is available indicating that lower DOX clearance resulting in a higher AUC is linked to complete remission in paediatric acute myeloid leukaemia (AML) [17]. Taken together, the paucity of well-designed randomized trials in the paediatric population provides only scarce evidence on the dose-concentration-effect relationships of anthracyclines in children. Our understanding of the consequences of pharmacokinetic (PK) parameters such as AUC and \( c_{\text{max}} \) for both toxicity and efficacy in paediatrics still remain insufficient. It has been suggested that the positive effect of continuous infusion seen in adult patients is attributed to a reduction of the cardiac anthracycline
concentration [10]. However, one might argue that in children with a developing heart, longer exposure due to prolonged infusion might be just as toxic as high peak concentrations.

Underscoring the high demand on more information on the PK and safety of DOX in paediatrics, the European Medicines Agency put DOX on their 2007 ‘priority list on studies for off-patent medicinal products’ supporting the conduct of further trials (doc. ref. EMEA/197972/2007, London, June 2007). Based on data from the EPOC-MS-001-Doxo trial Völler et al. demonstrated that the DOX clearance normalized to body surface area (BSA) is significantly lower in children below the age of 3 years compared to older children [18]. Though the physiological basis is unclear, the results of the EPOC trial raise the question whether the reduction of clearance and its effect on individual systemic therapy intensity is of direct clinical importance and should impact dosing recommendations. When looking at current treatment regimens in paediatrics, one is faced with a multitude of DOX doses, infusion times and instructions for dose adaptations [19, 20]. Obviously, protocols for children are rather based on empirical grounds than following a sound pharmacological rationale. Dose adaptations applied to infants and young children below a certain age or body weight are justified by the higher risk of late cardiac abnormalities in this patient group, yet age- and/or body weight-based boundaries and conversion rules from BSA-based dosing to body weight-based dosing are seemingly arbitrary. Again, considerable variability in systemic therapy intensity between individuals can be expected as a result from these dosing approaches.

Undoubtedly, with increasing numbers of childhood cancer survivors the prevention of cardiotoxic late effects must be given top priority. The reduction of variability in therapy intensity is essential. This also implies that the current practice of DOX administration needs to be critically questioned. As pointed out by Völler et al. the DOX population PK model provides an opportunity to develop rationale alternative dosing strategies reflecting PK characteristics [19]. However, due to the scarce evidence, the pharmacological goals of such a model-informed dosing recommendation can hardly be established solely upon existing data. In order to stimulate the discussion on the necessity and potential benefits of standardised DOX treatment regimens and to clarify the pharmacological goals of a future dosing recommendation we conducted a Delphi consensus procedure among experts in
paediatric oncology. This consensus process was accompanied and supported by simulations visualizing the impact of diverse treatment regimens and age-dependent differences in PK on therapy intensity.

Methods

**Pharmacokinetic simulations**

To visualize the impact of current dosing recommendations along with age-dependent differences in PK on drug exposure and peak concentrations Monte Carlo simulations were carried out using a population PK model published by Völler et al. [18]. The model was built upon PK data from 94 patients from the EPOC-MS-001-Doxo trial. This patient cohort was considered to represent typical paediatric cancer patients. Simulations of children aged 0 – 18 years with demographics taken from WHO and CDC growth charts were performed and DOX doses and infusion times from a selection of currently applied paediatric treatment regimens were analysed (see additional file 1) [21]. Individuals on the 5th, 50th or 95th percentile of body height and weight were simulated. Model parameters were fixed for simulations to the final parameter estimates of the EPOC patient population. To display the typical course of AUC and $c_{\text{max}}$ for a median child inter-individual and intra-individual variability were set to zero. Simulations including inter- and intra-individual variability were performed to display the remaining variability that cannot be explained by age and BSA. This variability represents the uncertainty associated with any model-based prediction. Each individual was simulated 1000 times.

In order to illustrate the effect of a standardized model-based dose calculation rule on drug exposure, observed AUC values for 94 patients from the EPOC cohort were compared with hypothetical, dose-adjusted AUC values. Calculation of dose-adjusted AUC values was based on a dose adaptation previously described by Völler et al. [19]. This dose adaptation takes individual age and BSA into account, as these parameters were identified as predictive covariates for DOX PK [18]. The goal of the suggested dose adaptation is to attain the AUC of an 18-year-old boy in children of all ages. Based on the model-predicted clearance $CL_{18 \text{ years}}$ for a typical 18-year-old boy with median demographics (equation 1 in the Supplementary Files), this target AUC$_{18 \text{ years}}$ was determined as 344 μg·L$^{-1}$·h for a
reference dose of 10 mg·m⁻² (1278 μg·L⁻¹·h for a reference dose of 1 mg·kg⁻¹ in case of body weight-based dosing). An adjusted DOX dose was obtained for each patient from the EPOC cohort according to equations 1 and 2. Firstly, the model-predicted clearance was estimated considering each patient’s age and BSA (equation 1). Secondly, the adjusted DOX dose was calculated (equation 2 in the Supplementary Files), where Dose₁₈ is the absolute DOX dose for the typical 18-year-old boy specified by the respective treatment regimen.

Based on the observed and adjusted DOX doses, observed and dose-adjusted AUC values were calculated according to equation 3 (see Supplementary Files) with CL_EPOC denoting the empirical Bayesian clearance estimates derived from the EPOC-MS-001-Doxo data.

To allow comparison across different treatment regimens and to illustrate deviations from the target, observed and dose-adjusted AUC values were normalised to the regimen-specific target AUC. Bias and precision were calculated for both groups as median prediction error and median absolute prediction error according to Sheiner and Beal [22]. The probability to attain a target range of 80 – 125 % was calculated for both groups. The range of 80 – 125 % around the target AUC was adopted from bioequivalence standards [23].

**Data and statistical analysis**

Monte Carlo simulations were carried out in NONMEM® version 7.3 [24]. R version 3.5.0 [25] and RStudio version 1.1.456 [26] were used for graphical representation of simulation results and statistical analysis. Non-parametric Wilcoxon signed rank test was performed on continuous data and McNemar’s chi-squared test was performed on paired nominal data. A p value < 0.05 was deemed statistically noticeable. Confidence intervals for the median were calculated using the function ‘quantileCI’ provided by the R package ‘jmuOutlier’ which calculates exact confidence intervals on quantiles based on the binomial test.

**Delphi consensus procedure**

The aim of a Delphi survey has been described to achieve consensus within a group of experts in an area with high uncertainty or a lack of empirical evidence. As a key feature, a Delphi survey is
designed as an iterative process based on a series of questionnaires and informed by a feedback of the groups’ responses which should encourage participants to reassess and, where appropriate, to change their opinions [27, 28]. The Delphi procedure consisted of three rounds. In a first qualitative pilot round participants were asked to answer a set of open-ended questions regarding pharmacological goals of DOX administration. The aim of this first round was to provide participants with a summary of relevant background information involving PK simulations and a description of current DOX administration schedules and to support the development of the definitive set of questions forming the 2\textsuperscript{nd} and 3\textsuperscript{rd} round questionnaires. In these two rounds more specific questions had to be answered by rating for agreement on a 5-point Likert scale (1 = strongly disagree; 5 = strongly agree) or for relevance (1 = not relevant; 5 = highly relevant), respectively. The 2\textsuperscript{nd} and 3\textsuperscript{rd} round questionnaires were structured in three sections covering (I) dose adaptations for infants/young children, (II) standardised dosing targets and (III) additional aspects that have been mentioned by the participants in the 1\textsuperscript{st} round (see additional file 2 for the 2\textsuperscript{nd} round questionnaire). Following round two responses were summarized and fed back to the participants within the third questionnaire. In view of the groups’ responses participants were asked to reassess their initial judgement and to re-rate all questions. Answering the questions was expected to take approx. 30 min for the 1\textsuperscript{st} and approx. 15 min for the 2\textsuperscript{nd} and 3\textsuperscript{rd} round questionnaire. The Delphi procedure is schematically represented in fig. 1. Three weeks after the initial distribution of each questionnaire a first reminder was sent and a subsequent reminder was sent two weeks later. Questionnaires and reminders were sent as emails. During the whole Delphi procedure, participants remained anonymous among each other. To maintain anonymity emails to the whole panel were sent as blind copies.

**Selection of panellists**

Overall, 28 experts in paediatric oncology from clinical centres in four European countries (France, Italy, Germany, United Kingdom) were invited to participate in this Delphi procedure. Invited experts were either EPOC consortium partners (20 experts) or representatives of linked clinical trials (8 experts). An invitation letter was sent to all panellists by email. Upon confirmation of participation the
first round questionnaire was sent.

**Analysis**

Qualitative content analysis was used to summarise responses from the first round questionnaire [29]. Responses were paraphrased and generalized to a first set of categories. Categories were then further reduced and summarized where appropriate. By coding all responses categories were refined. To control the adequacy of the final coding system this was repeated by a second group member. In case of disagreement the reason for disagreement was discussed and the coding system adjusted if necessary. Categories were then used to develop the definitive set of questions. Ratings from round two and three were summarized by specifying range and median. For each question the level of agreement was calculated as the combined percentage of ratings 4 and 5 on the 5-point Likert scale. If questions had not to be answered on a Likert scale (questions 5 & 6 in table 1) percentage of each individual answer was calculated. A level of agreement above 67 % was *a priori* considered as consensus.

**Results**

**Pharmacokinetic simulations**

Representative simulations visualising the impact of current DOX treatment schedules and age-dependent PK differences on systemic therapy intensity are illustrated. As outlined by fig. 2 exemplarily for three treatment regimens, substantial differences in drug exposure and peak concentrations have to be expected among children aged 0 – 18. In very young children who are subject to dose adaptations these may lead to particularly sharp steps in therapy intensity. For instance, simulated typical AUC and $c_{\text{max}}$ are lowest in neonates ($\text{AUC} = 507 \, \mu\text{g} \cdot \text{L}^{-1} \cdot \text{h}$, $c_{\text{max}} = 56 \, \mu\text{g} \cdot \text{L}^{-1}$) and increase towards a maximum in children slightly above one year of age ($\text{AUC} = 1002 \, \mu\text{g} \cdot \text{L}^{-1} \cdot \text{h}$, $c_{\text{max}} = 138 \, \mu\text{g} \cdot \text{L}^{-1}$) when treated according to the CWS-guidance (dose: 20 mg·m$^{-2}$, infusion time: 3 h). Here, the standard BSA-based dose is reduced in children < 1 year or weighing < 10 kg to 67 % (< 6 months) or 100 % (≥ 6 months) of the body weight-based dose (additional file 1). Due to age-
dependent differences in PK, therapy intensity can be expected to decrease with growing age. Taking the CWS-guidance as an example, simulated typical AUC decreases from its maximum 1002 µg·L⁻¹·h to 688 µg·L⁻¹·h at the age of 18. Similarly, however less pronounced, typical \( c_{\text{max}} \) decreases from 138 µg·L⁻¹ to 117 µg·L⁻¹.

Irrespective of schedule- and age-dependent variations a substantially broad distribution of individual AUC and \( c_{\text{max}} \) has to be considered due to the high variability in PK that cannot be sufficiently explained by age and BSA (fig. 3 A, B). As a result of conversion rules from BSA-based dosing to body weight-based dosing, therapy intensity will differ among infants of the same age but heterogeneous in body composition depending on the specific regimen-defined boundaries. For example, simulated median doxorubicin AUC and \( c_{\text{max}} \) differ more than 30 % between a one-year old child on the 95th percentile of body weight who already receives the full BSA-based dose according to the CWS-guidance and a child on the 5th or 50th percentile of body weight who still receives the body-weight-based dose (fig. 3 C, D). A comparison of simulated AUC and \( c_{\text{max}} \) following a single drug administration between selected treatment regimens is displayed in fig. 3 (E, F). Besides the dose, the duration of infusion determines peak concentrations leading to large differences between treatment regimens. Though the dose is lower in the NB 2016 N4 regimen (15 mg·m⁻²) compared to the CWS-guidance (20 mg·m⁻²) median peak concentrations simulated for a 2-year-old child are more than 3 times higher due to the difference in infusion time (30 min vs. 3 h).

Exemplarily, we assessed the impact of the dose adaptation that has been described by Völler et al. [19] on drug exposure for 94 children of the EPOC patient population (fig. 4). Application of this dosing algorithm allows to achieve a defined target AUC without relevant bias (-2.5 %, 95 % confidence interval -8 - 3 %), however, variability in drug exposure is still substantial underlined by the small decrease in precision between observed (21 %, 95 % confidence interval 18 - 23 %) and hypothetical, dose-adjusted AUC values (17 %, 95 % confidence interval 13 - 19 %) \( p < 0.05 \). The percentage of AUC attaining the range of 80 - 125 % around the target AUC was 58.5 % for the
observed AUC and 69.1 % for dose-adjusted AUC values. This difference was not statistically noticeable.

**Delphi consensus procedure**

The Delphi consensus procedure was conducted between September 2017 and April 2018. Overall, 28 experts were invited to participate in the Delphi procedure of whom 11 agreed to participate, one expert refused and 16 did not respond. Though 11 experts initially agreed to participate only 8 completed the first pilot phase questionnaire. The 2\textsuperscript{nd} and 3\textsuperscript{rd} round questionnaires were each completed by 11 experts. Both clinical centres (7 experts) and relevant paediatric study groups (4 experts) were represented in the final Delphi panel (fig. 1). In general, most questions were answered with high agreement among the panel members. For some questions, however, consent was marginally below or above the pre-specified threshold of 67 % with levels of agreement after round three of 64 % (7/11 ratings) to 73 % (8/11 ratings). Comparing outcomes from round two and three, trends in responses observed during round two were generally confirmed during the 3\textsuperscript{rd} round. The median score, range of scores and the level of agreement for the 2\textsuperscript{nd} and 3\textsuperscript{rd} Delphi round are summarised in tables 1 - 3.

*Dose adaptations for infants/young children*

Panel members generally acknowledged the clinical relevance of individual differences in systemic therapy intensity which arise from regimen-specific dose modifications as well as individual differences in PK. Nevertheless, dose adaptations are still considered necessary to reduce the risk of cardiac injury in the very young. To improve the current practice, experts agreed on a standardised a priori dose adaptation that takes into account patient’s age and BSA thus allows compensating for age-dependent differences in PK. The pharmacological goal of targeting equal AUC levels across the age range was deemed appropriate. Further, a reduction of peak concentrations in younger children was favoured, albeit only 8 out of 11 experts agreed. This could be achieved by a prolongation of infusion time in these children. As current conversion rules from BSA- to body weight-based dosing can be expected to cause arbitrary differences in therapy intensity among children of the same age
this should be avoided by future dose adaptations. Any reduction of the cardiotoxic risk in the high-risk population of very young children at the expense of a potentially lower tumour efficacy was not accepted by the majority of the panel members (table 1).

*Standardised dosing targets*

Chemotherapy regimens for childhood malignancies vary substantially in dose and infusion time with a large impact on systemic therapy intensity (fig. 3 E, F). Given the unclear role of PK characteristics such as AUC and $c_{\text{max}}$ we asked whether it might be desirable to target certain minimum and maximum therapy intensity thresholds, meaning in practice to constrain the range of currently applied doses and infusion times. The participating experts considered AUC, $c_{\text{max}}$ as well as the time of exposure to be important and favoured the establishment of both minimum and maximum threshold levels to balance the risk of cardiac side effects and tumour efficacy. We further asked whether such target ranges should be uniformly defined across different tumour entities. Here, outcome is not unequivocal as levels of agreement ranged from 64 % (7/11 ratings) to 73 % (8/11 ratings). Apart from *a priori* dose adaptations, all experts agreed that defined patient populations might additionally benefit from therapeutic drug monitoring approaches for DOX (table 2).

*Further aspects*

In their answers to the open-ended questions of the 1st Delphi round panel members raised additional aspects which were addressed in a separate section of the 2nd and 3rd round questionnaires. Adjusting DOX administration to the particular clinical needs of special patient populations was found to be relevant, which where infants/children with good prognosis disease, patients with tumour predisposition syndromes, Down syndrome patients with AML/ALL, and syndromes associated with higher toxicity of chemotherapy (e.g. Fanconi anaemia). Mediastinal/lung radiotherapy, pharmacogenetic analysis and use of liposomal DOX were considered as potentially relevant factors for DOX administration. Other co-medication and the use of a cardioprotectant were not regarded relevant (table 3).

*Discussion*

Among childhood cancer survivors, cardiac disease is the leading non-malignant cause for morbidity
and mortality [30]. As the vast majority of children diagnosed with cancer are currently cured [31], the prevention of treatment-related toxicities plays a key role. For DOX and other anthracyclines the relationship of PK measures (e.g. AUC, $c_{\text{max}}$) and treatment outcome has not been definitively established. The reduction of variability in treatment intensity holds promise to better balance tumour efficacy and the risk of toxicity, in particular late cardiac effects. Seemingly arbitrary thresholds for dose modification and conversion rules as part of empirically-derived treatment regimens along with age-dependent differences in individual PK substantially contribute to this variability. Protocol optimisation is needed and might offer the possibility to increase the safety of DOX administration. In a situation when definite clinical evidence is lacking a Delphi consensus procedure may help to sharpen the rationale and pharmacological goals of DOX dose adaptation in children with cancer. In contrast to open group discussions this approach permits collecting individual opinions and transforming opinions into a group consensus without being influenced by a single opinion leader [27]. The clinical experts who participated in this process agreed that individual differences in systemic therapy intensity are clinically relevant and the need to optimise current dosing recommendations was highly recognised. Though evidence is scarce, the Delphi procedure allowed clarifying the pharmacological goals of dose adaptations and formulating a standardised dosing concept, based on the collective knowledge and opinion of clinical experts. It should be clearly stated that collective opinion must not be erroneously confused with scientific evidence and should not be seen as indisputable fact. A Delphi procedure does not create new knowledge but rather seeks to make optimal use of already existing knowledge [27]. However, with the consented *a priori* dose adaptation a consistent strategy applicable to all treatment regimens has become available. The proposed concept individualises absolute DOX doses based on patient characteristics (age and BSA) that are predictive for DOX PK. Aiming at uniform drug exposure among children thereby appears to be most reasonable as systemic drug exposure has been widely used as a surrogate marker for dose adaptations [32]. An appropriate dosing equation is available based on the population PK model for DOX [19]. In this way optimised treatment regimens may allow for a rational choice of the DOX dose in paediatrics, ideally improving the safety of DOX application.
As a prerequisite for the proposed dosing concept the target AUC that should serve as reference needs to be specified. In our example we used the AUC expected for a ‘standard’ 18-year-old boy (i.e. an adult patient) as a reference (fig. 4), as this seems to be straightforward. However, other targets might be even more appropriate. For instance, a target AUC based on the median clearance of a representative patient population has been used for renal function-based carboplatin dosing [33]. The consented prolongation of infusion time in younger children as a measure to reduce peak concentrations might be opposed by clinical practicability (i.e. practicability in an ambulatory care setting) and patient convenience. In addition, the exact influence of infusion time on peak concentrations also requires further investigation.

Constraining the range of DOX doses and infusion times that are applied in current protocols may offer an opportunity to prevent extreme AUC values and, maybe more important, peak concentrations. As described above, a plethora of studies investigated the potentially beneficial impact of prolonged infusion (i.e. lower peak concentration) on cardiac outcome [10-12]. Based on a systematic review of the existing literature, Loeffen and colleagues recommended a DOX infusion duration of at least 1 h in paediatric cancer patients [34]. However, this conclusion does not take into account the administered dose and its impact on $c_{\text{max}}$. Additionally, some evidence is available pointing to an increased risk of heart failure with a higher maximal anthracycline dose within one week [4]. The avoidance of very short infusion times on the one hand or very high DOX doses on the other hand thus represents a potential measure to reduce the risk of long-term cardiac side effects. This has been unanimously consented by the expert panel but some disagreement arose from the question whether target ranges could be uniformly defined across different tumour types. In contrast to the large variety in DOX administration, there is no data that clearly demonstrate that different tumour entities indeed need specific peak concentrations or drug exposure. Yet, in multi-agent combination chemotherapy regimens adequate DOX therapy intensity will be influenced by the particular combination of chemotherapeutic drugs. Obviously, more research on the dose-concentration-effect relationships in different tumour types is needed to support the establishment of pharmacologically meaningful thresholds.
The approach presented herein underlines the value of population PK modelling for treatment optimisation. The DOX population PK model was used to illustrate the complex interplay of dose modifications and PK relationships. Moreover, it provides an opportunity to translate the consented dosing goals into alternative dosing algorithms. It has to be mentioned that the validity of the model-based approach is limited by the small number of patients below the age of one year recruited in the EPOC-MS-001-Doxo trial. Similar is true for highly obese paediatric patients. For a routine use of any model-based dosing recommendation two requirements are thus mandatory. Firstly, it is necessary to further validate the population PK model by assessing its predictive performance in a new patient population which should include relevant numbers of infants and young children [35]. Secondly, the consented dosing concept needs to be validated in a prospectively-designed clinical trial assessing its suitability to target a predefined drug exposure.

One may criticize that the Delphi expert panel was rather small to draw meaningful conclusions. However, standards for panel sizes have not yet been established and in the past, Delphi studies have been performed with virtually any panel size. With similar trained experts a small expert panel may be used with sufficient confidence [36]. Despite the small number of participants, agreement among the experts was strong with relatively little variation for most of the questions. The obtained consensus reflects the perspectives of both relevant paediatric study groups and clinical centres. Nonetheless, further discussion with clinical experts on the findings and potential implementations is highly welcome.

As suggested by fig. 4, a relatively small reduction in variability of drug exposure can be expected though individualisation of the DOX dose with respect to age and BSA. Large variability is a long-known characteristic of DOX PK. In adults, substantial inter-patient variations of AUC despite standardisation of the dose based on BSA were observed and differences in dose-normalised peak concentrations of more than 10-fold between children with ALL were reported in a study by Frost et al. [37–39]. Adaptive administration of chemotherapeutics based on plasma concentration measurements could provide an opportunity to further reduce variability in drug exposure. Individual PK parameters can be easily predicted based on a few plasma concentration measurements using a
Bayesian forecasting approach [32]. It has been shown before that adaptive dosing of chemotherapeutics can result in a narrower and more accurate exposure range compared with standard BSA-based dosing and can positively impact therapeutic outcome [40, 41]. However, in the past several studies revealed unpredictable differences in individual DOX PK between consecutive administrations [37, 42]. In a study by Hempel et al. in paediatric ALL and non-Hodgkin lymphoma patients intra-individual deviations in peak concentration ranged from 3.5 % to 198 % [42]. In accordance, population PK analysis of data from the EPOC-MS-001-Doxo trial found high intra-individual variability on the central volume of distribution [18]. Due to the high intra-individual variability Hempel et al. concluded that dose individualisation based on monitoring of peak concentrations will not be feasible. In contrast, in a population PK analysis in adults and children older than three years intra-individual variability of DOX clearance accounted only for 13 % [43]. As drug elimination might be less affected from intra-individual variability adaptive dosing approaches aiming to better control variability in drug exposure could indeed be promising. In fact, within the Delphi process the expert panel members acknowledged that therapeutic drug monitoring might be beneficial at least for defined paediatric patient populations.

Nevertheless, pre-analytical variability affects the uncertainties of pharmacokinetic models and model-based predictions. Further, the implementation of drug monitoring and adaptive dosing approaches in clinical routine is hampered by considerable technical effort and logistical requirements. The development of miniaturised monitoring tests and their delivery to the point-of-care is crucial to overcome these limitations [44].

Conclusions
Making use of the collective opinion of clinical experts the pharmacological goals of DOX dose adaptations have been specified. The consented a priori dose adaptation provides a consistent alternative to the huge diversity of current dosing recommendations for small children thus offering the chance to improve safety of this potent anticancer drug in the most vulnerable patient population. In perspective, the translation of any model-based dosing recommendation for DOX into clinical practice, regarding both a priori dose adaptations as well as adaptive dosing approaches, requires
consideration of several key aspects (table 4).

List Of Abbreviations
ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; AUC, area under the concentration-time curve; BSA, body surface area; $c_{\text{max}}$, peak concentration; DNR, daunorubicin; DOX, doxorubicin; PK, pharmacokinetics

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

Funding
There was no external funding for this study.

Authors’ contributions
Project idea and supervision: JB., CLK., GH

Simulations, Design of Delphi procedure and data analysis: CS, GW

Delphi panel: NA, FB, IC, PC, FD, ME, GE, MCF, NG, AG, AR

Manuscript writing: CS, GW, CLK, GH, JB

All authors contributed to and approved the final version of the manuscript.

Acknowledgements
The authors wish to thank Andrea Rademacher for her help in conducting and organising the Delphi process. The work presented herein is part of the PhD thesis of Christian Siebel.

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Tables
Table 1: Results of the Delphi consensus procedure (part 1).
| Question                                                                 | Median<sup>a</sup> | Range<sup>a</sup> | Level of agreement [%]<sup>b</sup> |
|------------------------------------------------------------------------|---------------------|-------------------|-----------------------------------|
|                                                                       | Round 2 3          | 2 3              | 2 3                               |
| 1 clinical relevance of age-dependent differences in plasma concentration-time curves | 5 5        | 3-5 4-5         | 82 100                            |
| 2 dose adjustment in infants to **reduce the risk of cardiac injury** | 4 4          | 2-5 3-5         | 82 91                             |
| 3 accept potentially lower tumour efficacy in favour of a reduced cardio-toxic risk | 3 3          | 2-5 2-5         | 27 9                              |
| 4 a priori dose adjustment to age and BSA to compensate individual differences in PK | 4 4          | 4-5 4-5         | 100 100                           |
| 5 adjust dose in infants/younger children to **achieve defined target**: |                        |                  |                                   |
| a) AUC uniform across age groups                                       |                     | 73 100           |                                   |
| lower in infants/younger children                                      |                     | 18 0             |                                   |
| not necessary to adjust to AUC                                         |                     | 0 0              |                                   |
| b) cmax uniform across age groups                                       |                     | 18 18            |                                   |
| lower in infants/younger children                                      |                     | 64 73            |                                   |
| not necessary to adjust to cmax                                        |                     | 18 9             |                                   |
| 6 further specification of alternative dose reduction strategies<sup>c</sup> |                     | equal AUC across age (option b) | 73 91 |
| 7 accept **age-specific adjustment of infusion time** within a given protocol to reduce cmax | 4 4 | 2-5 2-5 | 82 82 |
| 8 adjust dose to body composition to achieve uniform AUC/cmax in children of the same age | 4 4 | 2-5 4-5 | 82 100 |
PK, pharmacokinetic; AUC, area under the concentration-time curve; cmax, peak concentration

a On a 5-point Likert scale (1 = strongly disagree; 5 = strongly agree)

b Combined percentage of ratings 4 and 5 on the 5-point Likert scale

c For question 6 only the most selected option is shown

Table 2: Results of the Delphi consensus procedure (part 2).

| Question                                                                 | Median\(^a\) | Range\(^a\) | Level of agreement [\(^\%\)]\(^b\) |
|-------------------------------------------------------------------------|--------------|-------------|----------------------------------|
|                                                                          | Round 2      | 3           | 2      | 3           | 2      | 3           |
| 9  | establish **maximum-allowed PK targets** to reduce the risk of cardiotoxic side effects | 4 4 4-5 4-5 100 100 |
|    | maximum-allowed AUC                                                      | 4 4 4-5 4-5 100 100 |
| 10 | establish **minimum-allowed PK targets** to guarantee appropriate tumour efficacy | 4 4 1-5 4-5 91 100 |
|    | minimum-needed AUC                                                      | 4 4 2-5 4-5 82 100 |
|    | minimum-needed cmax                                                    | 4 4 2-5 4-5 82 100 |
|    | minimum needed time over threshold                                      | 4 4 3-5 4-5 91 100 |
| 11 | establish **uniform targets across different tumour entities/treatment protocols** | 4 4 2-5 2-4 64 73 |
|    | uniform target AUC                                                     | 3 4 2-5 2-4 45 64 |
|    | uniform target cmax                                                    | 4 4 2-5 2-4 55 73 |
| 12 | therapeutic drug monitoring of doxorubicin to provide additional benefit for defined patient populations | 5 5 4-5 4-5 100 100 |
PK, pharmacokinetic; AUC, area under the concentration-time curve; cmax, peak concentration

a On a 5-point Likert scale (1 = strongly disagree; 5 = strongly agree)

b Combined percentage of ratings 4 and 5 on the 5-point Likert scale

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**Table 3: Results of the Delphi consensus procedure (part 3).**

| Question                                                                 | Median<sup>a</sup> | Range<sup>a</sup> | Level of agreement [%]<sup>b</sup> |
|-------------------------------------------------------------------------|---------------------|-------------------|-----------------------------------|
| **Round 2**                                                             | 3                   | 2                 | 3                                 |
| 13 relevance of adapting doxorubicin dosing to special patient populations<sup>c</sup> |                     |                   |                                   |
| · infants/children with good prognosis disease                          | 4                   | 4                 | 4-5                               |
| · tumour predisposition syndromes                                        | 4                   | 4                 | 1-5                               |
| · Down syndrome patients with AML/ALL                                   | 5                   | 5                 | 4-5                               |
| · syndromes with higher toxicity of chemotherapy                         | 5                   | 5                 | 4-5                               |
| 14 relevance of further individual patient characteristics for doxorubicin dosing |                     |                   |                                   |
| · use of cardioprotectant                                               | 3                   | 3                 | 1-5                               |
| · other co-medication                                                   | 4                   | 4                 | 1-5                               |
| · mediastinal/lung radiotherapy                                          | 5                   | 5                 | 2-5                               |
| · pharmacogenetic analysis<sup>d</sup>                                   | 4                   | 4                 | 2-5                               |
| · use of liposomal doxorubicin                                           | 4                   | 4                 | 2-5                               |

PK, pharmacokinetic; AUC, area under the concentration-time curve; cmax, peak concentration

a On a 5-point Likert scale (1 = not relevant; 5 = highly relevant)

b Combined percentage of ratings 4 and 5 on the 5-point Likert scale

c Additional patient populations have been suggested by the participants during round two: neuroblastoma patients (low/intermediate vs. high risk), frail patients and obese patients
Suggested pharmacogenetics markers include polymorphisms in genes encoding for carbonyl reductases, ABC transporters, catalase, nitric oxide synthase, solute carrier transport proteins, and superoxide dismutase.

Table 4: Key aspects that need to be considered for clinical implementation of model-based dosing recommendations.

|   | Development and implementation of miniaturised bedside analytics in order to minimise pre-analytical variability and facilitate drug monitoring |
|---|-----------------------------------------------------------------------------------------------------------------------------------------|
| 2 | External validation of pharmacokinetic models and, if appropriate, further refinement in order to assess the predictive power and decrease the uncertainties of model predictions |
| 3 | Development of optimised limited sampling strategies to keep the burden of blood sampling for children at a minimum |
| 4 | Clinical validation of model-based dosing recommendations in a prospectively designed clinical trial |

Additional Files

Additional file 1: Table S1. Overview on doxorubicin doses, infusion times and dose modifications in young children for selected treatment regimens. (DOCX 40kb)

Additional file 2: Questionnaire S2. Questionnaire for the second round of the Delphi procedure. (PDF 1.2 MB)

Figures
Figure 1

Schematic representation of the Delphi consensus procedure. Overall 28 experts representing paediatric study groups or clinical centres from the EPOC-MS-001-Doxo trial were invited to participate in the Delphi procedure of whom 8 answered the 1st round questionnaire and 11 answered the 2nd and 3rd round questionnaire, respectively. The final Delphi panel represents relevant paediatric study groups (4 out of 8 invited experts; response rate 50 %) and clinical centres (7 out of 20 invited experts; response rate 35 %).
DOX AUC (A) and cmax (B) across the age range from 0 to 18 years. Typical AUC and cmax values were simulated for children on the 50th percentile of body height and weight for three selected treatment regimens. Underlying DOX doses were adjusted as specified by the respective regimen (additional file 1). For the AIEOP-BFM ALL 2017 protocol only children ≥ 1 year were simulated according to the inclusion criteria of the study.
DOX AUC and cmax depending on age (A,B), body composition (C,D), and treatment regimen (E,F). For (A,B) children on the 50th percentile of body height and weight were simulated and for (C,D) children aged 1 year were simulated. The DOX dose was adopted
from the CWS-guidance. For (E,F) a median 2-year-old child was simulated (for doses and infusion times see additional file 1). To display the remaining inter-individual variability that cannot be attributed to the influence of age or body surface area simulations were replicated 1000 times.
Comparison of observed AUC from 94 patients from the EPOC-MS-001-Doxo trial and dose-adjusted AUC. Adjusted DOX doses were derived from a model-based dose calculation rule. AUC values were calculated based on the post-hoc clearance estimates taken from the NONMEM analysis and normalised to the target AUC of a typical 18-year-old boy. The dashed red line indicates the target AUC of 100 % and dotted red lines indicate a range of 80-125 %.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

Equations.jpg
Additional File 1.pdf
Additional File 2.pdf