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ORIGINAL ARTICLE

Cyclophosphamide dose adjustment based on body weight and albuminemia in elderly patients treated with R-mini-CHOP

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Abstract

Background Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma in elderly patients, and R-CHOP chemotherapy is the standard treatment protocol for DLBCL. Elderly patients (often defined as 75 years of age) are treated with anticancer drugs with precaution; however, the pharmacokinetics and pharmacodynamics (PK and PD) of these agents have not been thoroughly investigated in this population. In this study, we investigated the PK of cyclophosphamide (CP) and doxorubicin (DOXO) in elderly patients in order to verify if there is an influence of age on the PK of these anticancer drugs.

Materials and methods This is a prospective multi-center clinical trial investigating the PK of CP and DOXO in elderly and very elderly patients with DLBCL treated by R-mini-CHOP regimen. Dose levels were 25 mg/m^2, 0.7–1.4 mg/m^2, 750 mg/m^2, and 375 mg/m^2 for DOXO, Vincristine (VCR), CP, and Rituximab, respectively. For PK analysis, 7 time point samples were collected over 48 h post-administration on cycle 3. CP and VCR plasma concentrations were measured using UPLC–MS/MS validated method. DOX plasma concentrations were measured using UPLC coupled with fluorescence detection-validated method. PK-POP modeling has been performed with a non-linear mixed-effect model program (Monolix).

Results 31 patients (15 males and 16 females), 75 to 96 years old, were treated with R-miniCHOP protocol. Among them, 19 patients were treated with VCR. A one-compartment (1cpt) open model with linear elimination adequately described CP concentration–time courses. The population PK parameters for CP were: CL = 3.58 L/h, Vmale = 32.2 L, and Vfemale = 28.7 L. Body weight (BW), albuminemia, and gender demonstrated a significant impact on CP PK. A 2-compartment (2cpt) open model with linear elimination best described DOXO concentration–time courses. The population PK parameters for DOXO obtained for the structural model were: CL = 51.1 L/h, Q = 49.6 L/h, V1 = 29.4 L, V2 = 1,130 L (clearances: CL, Q, volumes of distribution: V1, V2). The main covariate effects on DOXO PK were related to gender, BW, and VCR administration. VCR increases DOXO V1 from 29.4 L to 57.5 L ($p = 0.02$). No hematologic and cardiac grade 3 or 4 toxicity were recorded.

Conclusions Usually, in the absence of specific data, the majority of the physicians empirically reduce anticancer drug dose in the elderly patients (Tourani in J Geriatr Oncol 3(1): 41–48, 2012), or even does not treat these very-old patients. A better knowledge of the pharmacokinetics in very-old patients should allow a better dose adjustment based on the most significant physiological factors that modify the pharmacokinetic parameters. In this study, no serious toxicity was observed in these very elderly patients (84.1 years). This indicates that dose adjustment of chemotherapies should not only be based on age and creatinine clearance, but also, based upon appropriate physiological and biological data. Our findings indicate that, CP dose adjustment should be done according to serum albumin levels and patients BW and gender.

Keywords Eldelrly patients · R-mini-CHOP · Pharmacokinetics · Dose adjustment

Introduction

The World Health Organization [1] and United Nations [2] project an increase in the number of people aged 65 years and older from around 524 million in 2010 to nearly 1.5 billion in 2050, particularly in developing countries [3].

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Between 2000 and 2050, global life expectancy rates are expected to increase from 65 to 74.3 years old [3, 4].

In Europe, 60% of cancers and 75% of cancer deaths occur in patients over 65 years of age. The incidence of certain cancers such as prostate, colorectal and hematological malignancies increases with the age advancement. Among them, lymphoma has an incidence of 99/100,000 per year and more particularly non-Hodgkin's lymphoma. They account for about 4.5% of malignancies. It increased steadily from 8.5 to 16/100,000 in developed countries over the last 20 years. The gender ratio (male/female) is 1.5/1. In Europe and North America, more than 50% of non-Hodgkin's lymphoma cases occur in patients over 65 years of age [5]. It is, therefore, a frequent oncological pathology of the elderly.

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma in older patients and R-CHOP chemotherapy (cyclophosphamide (CP), doxorubicin (DOXO), vincristine, and prednisolone in combination with rituximab) is the standard treatment protocol for DLBCL. Older patients (often defined as over 75 years of age) are treated with anticancer drugs with precaution; however, the pharmacokinetics and pharmacodynamics (PK and PD) of these agents have not been thoroughly investigated in this population.

The utilization of chemotherapeutics agents in elderly people requires a better knowledge of pharmacological modifications due to age and diversity in this population. For example, cellular senescence could reduce the possibility for normal tissues to be repaired after chemotherapy. Similarly, changes in fat-to-lean body mass ratio could influence anticancer drugs PK in elderly patients. Moreover, tumors in elderly patients could be more resistant to chemotherapy because of a more frequent expression of the mdr-1 gene or abnormalities in P-53 or bcl-2 genes [6]. Furthermore, comorbidities also modify patient physiology, which leads geriatricians to classify patients into « fit », « fragile » or « dependent » patients.

These multiple physiological changes in elderly patients may influence the PK parameters of anticancer drugs, including absorption, distribution, metabolism and elimination (ADME) as well as drug PD. Therefore, prospective trials need to be conducted to study in depth drugs PK and PD properties in the elderly and establish PK–PD relationships in this specific population [7].

To our knowledge, this is the first study performing a population pharmacokinetic (POPPK) modeling of cyclophosphamide (CP) and doxorubicin (DOXO) in very old DLBCL patients (mean age 84.1 years).

The aim of this study was to evaluate the influence of biological and/or nutritional factors on the PK parameters of CP and DOXO in non-Hodgkin's lymphoma B large cell patients treated with R-mini CHOP poly-chemotherapy regimen.

Patients and methods

Design

A prospective multi-center clinical trial investigating the PK of CP and DOXO in old and very old DLBCL patients was conducted according to ethical principles and in accordance with Good Clinical and Laboratory Practices. The Ethics Committee (CPP IDF VI—Pitié Salpétrière) approved the protocol and its amendments. All patients provided written informed consent. Patients were treated with a R-mini CHOP chemotherapy regimen. Patients received 25 mg/m^2, 0.7–1.4 mg/m^2, 750 mg/m^2 and 375 mg/m^2 of DOXO, Vincristine, CP and Rituximab, respectively.

Eligibility criteria

Patients older than 75 years without upper limit of age, with a cytologically or histologically confirmed diagnosis of DLBCL, eligible for R-mini CHOP chemotherapy for the first line of treatment were enrolled.

Patients with severe dementia (MMS < 10), patients under legal protection, patients with a pace-maker, patients with severe renal impairment (creatinine clearance, according to Cockroft–Gault formula < 30 mL/min), and patients with concomitant medication known to interact with R-CHOP regimen were not enrolled in the study.

Sampling schedule

For PK analysis, seven blood samples were collected before dosing and 20 min, 75 min, 4 h, 5.5 h, 24 h and 48 h after the start of R-mini CHOP administration during cycle 3.

Geriatric assessment

A geriatric assessment, evaluating comorbidity, concomitant disease, and functional status, was performed for each patient before starting R-mini CHOP treatment. Physiological and biological data such as age, weight, body surface area, hemogram, albumin, creatinine, urea, BNP, CRP, and hepatic balance were recorded before treatment cycle 1 and cycle 3. Toxicity (neutropenia, thrombocytopenia, febrile neutropenia, cardiac toxicity) and survival were assessed at the beginning of the 4th cycle. Body composition data were obtained by absorptiometry.

Analytical methods

CP concentrations were determined using a validated Acquity Ultra Performance LC system (Waters, Milford, MA, USA) coupled with a tandem mass spectrometry detection method, as described previously [8]. The lower limit of quantification

of CP was 5.0 ng/mL, with 6.0% precision and 90.0% accuracy. DOXO concentrations were determined using a validated Acquity Ultra Performance LC system (Waters, Milford, MA, USA) coupled with a fluorescence detection method, as described previously [9]. The lower limit of quantification of DOXO was 2.5 ng/mL, with 8.7% precision and 106% accuracy.

Pharmacokinetic modeling

Data were analyzed using the nonlinear mixed-effect modelling software program Monolix (http://wfn.software.monolix.org). Parameters were estimated by computing the maximum likelihood estimator of the parameters without any approximation of the model (no linearization) using the stochastic approximation expectation maximization (SAEM) algorithm combined to a Markov Chain Monte Carlo (MCMC) procedure. A proportional model was used to describe the residual variability and the inter-individual variabilities (IIV) were described as an exponential model.

The main continuous covariates tested were:

(a) body size descriptors

Given that patients treated in this study had a wide range of body weight, different size descriptors were investigated, such as total body weight (BW), ideal body weight (IBW) and lean body mass (LBM) [10],

$$\text{IBW} = \text{Height (cm)} - (105 \text{ if women or } 100 \text{ for men})$$

$$\text{LBM} = y \times \text{Weight (kg)} - z \times (\text{Weight}/\text{Height})^2$$

with $y = 1.07$ and $z = 148$ for women and $y = 1.1$ and $z = 128$ for men

(b) Albuminemia

(c) Hemoglobin level

The main categorical covariates tested were:

1. Gender
2. Co-administration of vincristine (12 patients were not treated by vincristine according to their baseline hematological status).

Concentrations below the limit of quantification were considered as missing data and were not included into the model.

At each step of the model building, a candidate model was accepted or rejected on the basis of the Bayesian information criterion (BIC), which is the most conservative test. Moreover, standard goodness-of-fit plots [observed concentrations versus population- and individual-predicted concentrations, individual and population-weighted residuals, and the visual predictive check (VPC) based on 1000 simulations] were used to appreciate the curve-fitting.

Results

Demography

From April 2013 to September 2015, 31 patients (15 males, 16 females) were treated with R-mini CHOP protocol. Baseline characteristics of patients are summarized in Table 1. The median age is 85 years. Two groups of ages were defined: the "old" 75–84 years, and the "very old" > 85 years. Among 31 patients who were enrolled in this study, 19 patients were treated with vincristine.

Pharmacokinetics

The POPPK modeling was performed using the dataset obtained on treatment cycle 3 from 31 patients. A total of 134 and 120 concentrations for DOXO and CP were available for PK-POP modeling, respectively. Five DOXO concentrations were below limit of quantification and were considered as missing data.

Cyclophosphamide PK

A one-compartment (1cpt) open model with linear elimination adequately described CP concentration–time courses. IIV was estimated for clearance (CL). BW was the best size descriptor when CL and V terms were normalized to a standard BW of 70 kg according to an allometric scaling rule. Also albuminemia had a significant ($p = 0.0199$) impact on CP CL according to the following equation:

$$\text{CL}_i = \text{CL}_{\text{POP}} * \left(\text{BW}_i/70\right)^{0.75} * \left(\text{ALB}_i/40\right)^{0.39}$$

where the subscripts "i" and "POP" denote the individual and average population parameters.

The final model was validated according to the BIC drop, as well as the IIV decrease relative to the covariate-free

Table 1 Baseline patient characteristics

Parameters	Mean	Median	Minimum–maximum
Age (years)	84.1	85	75–96
BW (kg)	64.5	63	41–112
Height (cm)	164.8	163	150–190
BSA (m^2)	1.7	1.7	1.32–2.3
BMI (kg/m^2)	23.5	23.7	17.9–34.6
LBM (kg)	48.6	47.7	32.8–73.6
IBW (kg)	62.3	62	45–90
HB (g/L)	11.6	11.9	9.1–14
Serum albumin	36.3	36	19–47
Serum creatinine (mol/L)	77.3	77	45–180

BW body weight, *BSA* body surface area, *BMI* body mass index, *LBM* lean body mass, *IBW* ideal body weight, *HB* hemoglobin

model (0.158 vs 0.178). VPCs showed the good predictive performance of the final model (Fig. 1).

CL values of CP were similar for old and very old population (3.58 L/h and 3.23 L/h respectively; $p = 0.34$, Fig. 2). Moreover, a significant difference ($p = 0.013$) was observed between CP volume of distribution in men and in women.

In the final model, V and CL average estimates were 32.2 L and 3.58 L/h, respectively (RSEs 4.1, and 3.5%, respectively) and the corresponding IIV for CL was 0.158.

In "Appendix 1", a R code is written to easily determine a dose adaptation given the CP population clearance and individual values of body weight and albuminemia.

Doxorubicin PK

A two-compartment (2cpt) open model with linear elimination best described DOXO concentration–time courses. IIV was estimated for CL and V1. Among covariates, BW was the best size descriptor when CL and V terms were normalized to a mean BW of 70 Kg according to an allometric

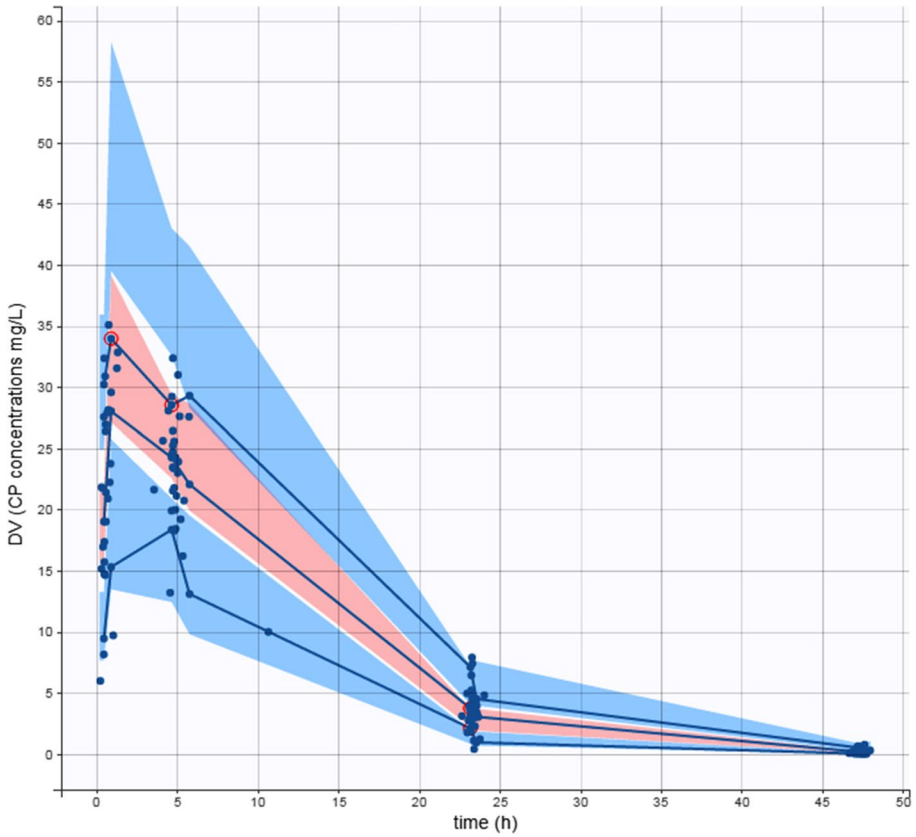


Fig. 1 Visual predictive check for the final plasma CP population model. The blue lines represent the 5th, 50th and 95th percentiles of the observed concentrations. The corresponding bands denote the 90% confidence interval from 1000 simulated samples. The blue dots correspond to observed values

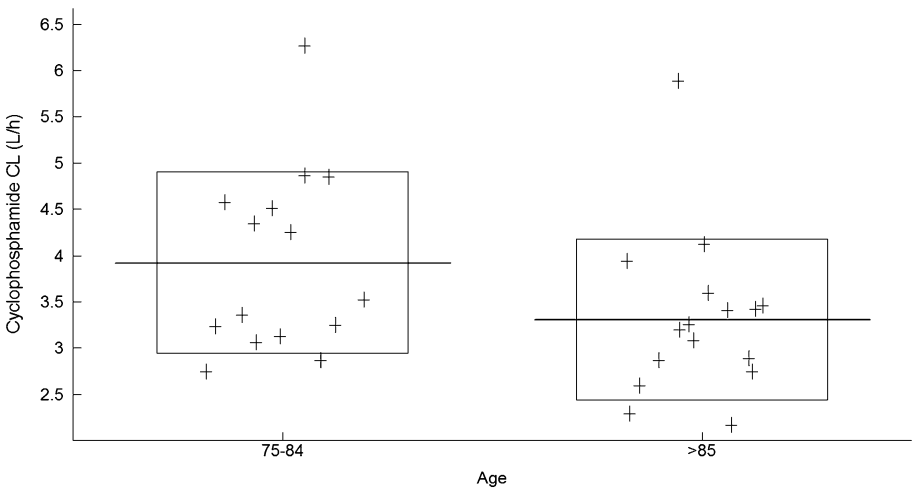


Fig. 2 Comparison of CP CL values (L/h) between elderly and very elderly patients, one-way ANOVA test ($p = 0.34$)

scaling rule. Patient's gender had a significant ($p = 0.014$) impact on DOXO CL according to the following equation:

$$CL_i = CL_{POP} * \left(BW_i/70\right)^{0.75} * e^{\beta} \quad \text{with}$$
$$\beta = -0.21 \text{ for women and 0 for men,}$$

where the subscripts "i" and "POP" denote the individual and average population parameters.

Co-administration of vincristine had a significant influence ($p = 0.008$) in the V_{DOXO} according to the following equation:

$$V_i = V_{POP} * (BW/70)^1 * e^{\beta} \quad \text{with } \beta_{vincristine} = 0.67,$$

where the subscripts "i" and "POP" denote the individual and average population parameters.

The goodness of fit plots (Fig. 3) and VPC (Fig. 4) for the final DOXO model clearly showed the improvement of fit from the covariate-free model to the final model (base model plots not shown). Estimated DOXO PK parameters such as total plasma CL, inter-compartmental clearance (Q), central and peripheral volumes of distribution (V1 and V2) were 51.1 L/h, 49.6 L/h, 29.4 L and 1,130 L, respectively. IIV estimates were 0.19 and 0.52 for CL and V1. The IIV decreases relative to the covariate-free model (0.19 vs 0.29 and 0.52 vs 0.95 for CL and V1, respectively). DOXO CL seemed ($p = 0.06$) to be lower in very old patients (> 85 years) than in elderly patients (< 85 years) (Fig. 5).

PK parameters of CP and DOXO on cycle 3 are summarized in Tables 2 and 3, respectively.

Safety

In this clinical trial, all patients included in the 3rd cycle were alive at the beginning of the 4th cycle of R-miniCHOP regimen. No hematologic and cardiac grade 3 or 4 toxicities were recorded. The main hematological toxicities observed were: grade 1 and 2 anemia and thrombocytopenia.

Discussion

PK of chemotherapies has been widely described in adults younger than < 75 years, whereas very few clinical studies have focused on the PK of these molecules in elderly patients since this population is usually excluded from clinical trials due to comorbidities, co-medication, performance status and cognitive disorders [11, 12].

Aging alters multiple physiological functions such as an increase in fat-to-lean mass ratio, which could affect the PK of anticancer drugs. We report here for the first time the POPPK of CP and DOXO in very old patients with DLBCL. Their mean age, 84.1 years, is representative of a typical population of geriatric service.

As described previously [13, 14], a one-compartment open model with linear elimination adequately described CP concentration versus time course in elderly and very elderly patients. The VPC shows an apparent model over-prediction of CP in the end of infusion; however, this occurs only for the higher percentile (90th) of observations/predictions and in the

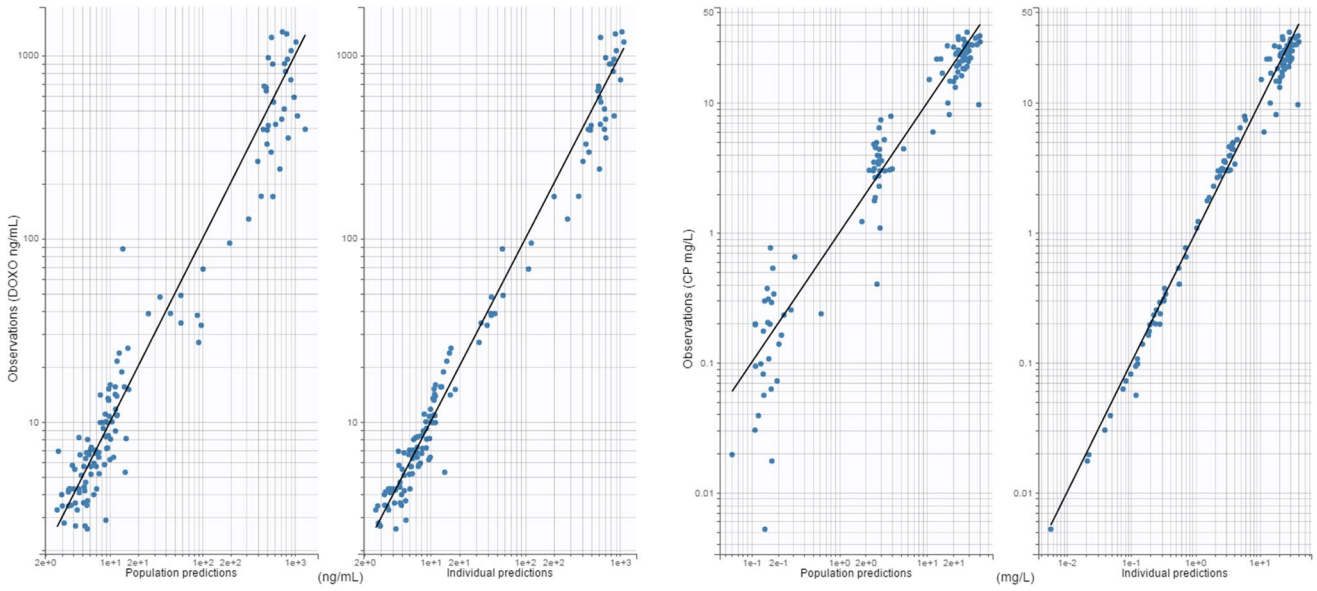


Fig. 3 Goodness-of-fit plots. Observed DOXO and CP concentrations (DV) versus model predictions. Diagnostic plots of observed (obs) DOXO concentrations (left panel) expressed in ng mL^{-1} and CP concentrations (right panel),expressed in mg/L, versus the model population predictions (pop pred left) and individual predictions (ind pred right) for thefinal model. The blue dots correspond to observed values, Identity line ($y = x$ line)

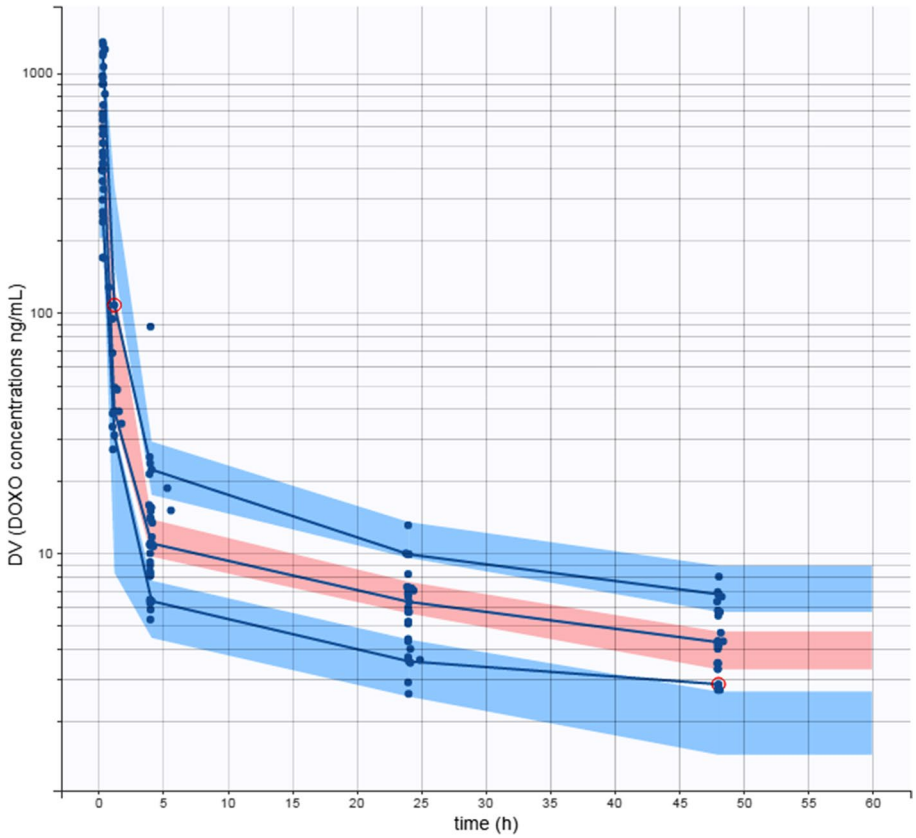


Fig. 4 Visual predictive check for the final plasma DOXO population model ($p=0.06$). The blue lines represent the 5th, 50th and 95th percentiles of the observed concentrations. The corresponding bands denotethe 90% confidence interval from 1000 simulated samples. The blue dots correspond to observed values

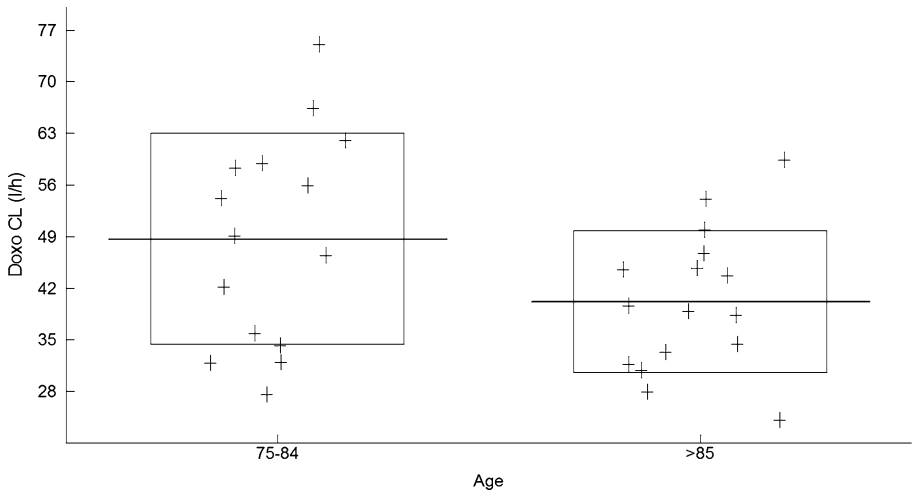


Fig. 5 Comparison of DOXO CL values (L/h) between elderly and very elderly patients, one-way ANOVA test

short 5 h post-infusion. This stands for only a short segment of the concentration–time course and could be due to little inaccuracies in the sampling times. The present PK analysis in 31 patients showed that albuminemia had a positive effect on CP CL (1% per 1 g/L albumin, $p=0.02$). Higher albuminemia could reflect a better hepatic function and, therefore, a higher CP CL. Our findings are in agreement with the results reported by Wilde et al. in a younger population cohort (17–59 years). We did not observe significant difference ($p=0.2$) of CP CL between the elderly (75–84 years) and very elderly (> 85 years) patient groups. However, the mean value of CP CL in our study (3.58 L/h) is lower than the one obtained by Wilde et al. (4.29 L/h) [13] and Joerger et al. (4.23 L/h) [14] in younger patients (mean age 34 years and 56 years for Wilde and Joerger, respectively). There is no significant difference of CP PK between patients receiving or not receiving vincristine.

The PK of DOXO has been well documented in younger patients [15, 16]. A two-compartment open model with linear elimination best estimated DOXO POPPK parameters. A similar PK model was used in younger adults by Wilde et al. and Joerger et al. [13, 14]. The calculated PK parameters values in the present study are in accordance with previous

Table 2 Final model estimated population pharmacokinetic parameters of CP

Parameters	Covariate effect	Estimate (RSE %)	IIV (RSE %)
CL (L/h)/40 g/L, 70/kg	$(ALB/40)^{\beta}$ $(BW/70)^{0.75}$	3.58 (4.1) $\beta_{ALB} = 0.43$	0.158 (13.8)
V (L)/70/kg, men	$(BW/70)^{1}$	*V*(m) = 32.2 (4.1) *V*(f) = 28.7 $\beta_{sex} = -0.115$	NA
Residual variability proportional		0.269 (7.6) sd = 0.02	NA

RSE% percent relative standard error, *IIV* inter individual variability, *sd* standard deviation, *V* volume of distribution, *CL* clearance, *ALB* serum albumin, *HB* hemoglobin, *NA* not applicable, *m* male, *f* female; proportional model was applied for the random effects

Table 3 Final model estimated population pharmacokinetic parameters of DOXO

Parameters	Covariate effect	Estimate (RSE %)	IIV (RSE %)
CL (L/h)/70/kg, men	$(BW/70)^{0.75} * EXP^{\beta_{sex}}$	CL(m) = 51.1 (6.66) CL (f) = 41.4 $\beta_{sex} = -0.21$	0.19 (19)
V1 (L)/70/kg, without vincristine	$(BW/70)^{1} * EXP^{\beta_{vin}}$	V1 = 29.4 (19) V1 (vin) = 57.8 $\beta_{vin} = 0.67$	0.58 (17)
Q (L/h)/70/kg	$(BW/70)^{0.75}$	49.6 (7.9)	NA
V2 (L)/70/kg	$(BW/70)^{1}$	1130 (9.0)	NA
Residual variability proportional		0.309 (8.2) sd = 0.025	NA

RSE% percent relative standard error, *IIV* inter individual variability, *CL* total plasma clearance, *V1* central volume of distribution, *Q* inter-compartmental clearance, *V2* peripheral volume of distribution, *NA* not applicable, *m* male, *f* female, *vin* vincristine, proportional model was applied for the random effects

reports [14, 17]. We observed that DOXO CL was significantly higher in men than in women (51.1 L/h vs 41.4 L/h, $p = 0.014$) as it was reported by Dobbs et al. [18]. This is probably due to higher LBM values in men than in women in our study. This is consistent with published data demonstrating the correlation between LBM and DOXO PK [19]. Interestingly, in this study BW was the best size descriptor for CL and V terms. Moreover, PD parameters such as toxicity were similar in men and women populations. Finally, a trend of DOXO CL decrease with age was observed in accordance with previously published data in younger patients [20].

The DOXO analysis showed that that vincristine administration increases DOXO central volume of distribution and by the way, may explain V1 inter-individual variability in old and very old DLBCL patients in the RCHOP regimen. The use of vincristine in combination chemotherapy with DOXO could decrease hepatic metabolism of DOXO due to higher affinity binding of P-gp by vincristine [21]. In fact, Ambukdkar et al. [22] demonstrated that in liver, P-gp is present on the biliary side of hepatocytes, consistent with the role of P-gp in the excretion of xenobiotics and endogenous metabolites into the bile. Interestingly, a significant difference of DOXO V1 was observed when we compared DOXO V1 values for patients who received vincristine with patients without vincristine administration ($p = 0.008$). As previously reported by Li et al. [20], we observed no influence of advanced age on the DOXO central volume of distribution which is consistent with data published by Li et al. [20]. The major limitation of the study is the relatively small number of patients (31) and the lack of reference group of younger patients (< 75 years). This could explain the lack of significant age-related effect on the PK of DOXO and CP in very old patients. Indeed, this study was originally designed to compare PK behavior of R-mini CHOP regimen administered to two groups of patients with DLBCL (30 patients < 75 years versus 30 patients > 75 years of age). Unfortunately, due to inclusion difficulties, only patients over 75 years of age were included in this study. Moreover, the reduced number of plasma samples after 30 h and the lack of doxorubicinol concentrations could explain that the three-compartment model is not as accurate as previous published ones.

The present report provides new insights into the PK of R-mini CHOP regimen administered to old and very old cancer patients.

Conclusion

Usually, in the absence of specific data, the majority of the physicians empirically reduce anticancer drug dose in elderly patients [23], or even does not treat this patient population. A better knowledge of the PK in very old patients should allow a better dose adjustment based on the most significant physiological factors that modify PK parameters. In this study, no serious toxicity was observed in very elderly patients (84.1 years). This indicates that dose adjustment of chemotherapies should not only be based on age and

creatinine CL, but also, based upon appropriate physiological and biological data. Our findings indicate that CP dose adjustment should be done according to serum albumin levels and patients' BW.

Based on this PK analysis the recommended CP dose adjustment using the R code is:

1. 750 mg/m^2 for patient with BW = 70 kg and albuminemia = 40 g/L.
2. 365 mg/m^2 for cachectic patient with BW = 40 kg and albuminemia = 20 g/L.
3. 1140 mg/m^2 for patient with BW = 110 kg and albuminemia = 47 g/L.

Author contributions Concept and design: EB, PC, KR. Data collection: EB, AL. Couderc, analysis and interpretation of data: SH, FB, SW, OM, KR. Manuscript writing and approval: EB, CV, SU, KR.

Compliance with ethical standards

Conflict of interest None of the authors has conflicts of interest directly related to the contents of this review.

Appendix 1

R code for dosing adaptation. Appendix Figure shows examples.

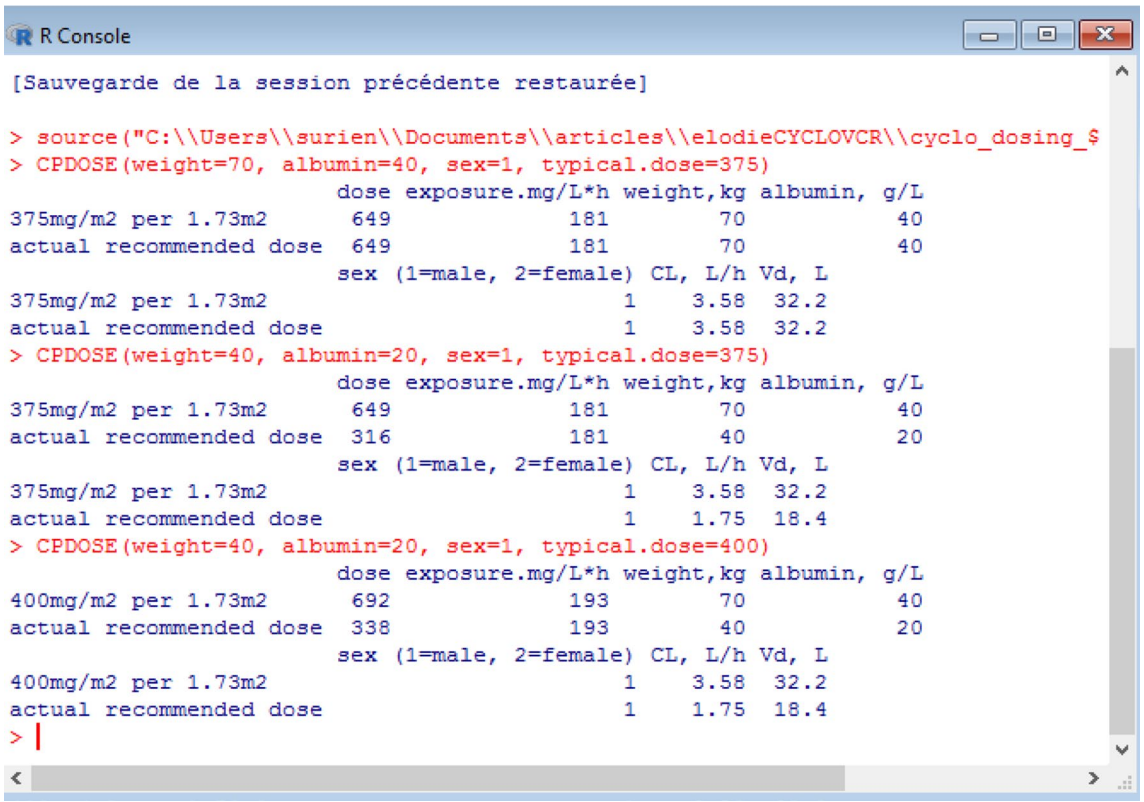
```
CPDOSE <- function(weight=70, albumin=40, typical.dose=750){
       pars <- function(weight=70, albumin=40){
              CL<-c(3.58)*(albumin/40)^0.43*(weight/70)^0.75
              return(c(CL=CL))
       }
       xx  <- pars()
       xxx <- pars(weight=weight, albumin=albumin)
       typdos <- typical.dose*1.73
       typxpo <- typdos/xx
       dosex <- xxx[1]*typxpo
       dx <- data.frame(dose=c(typdos,dosex),
                                expo=c(typxpo,dosex/xxx[1]),
                                weight=c(70,weight),
                                albumin=c(40,albumin),
                                CL=c(xx[1], xxx[1])
                                 )
       names(dx)<-c("dose","exposure.mg/L*h","weight,kg","albumin, g/L","CL, L/h")
       rownames(dx) <- c(sprintf("%.3gmg/m2 per 1.73m2",typical.dose),"actual
recommended dose")
       print(dx, digits=3)
}

## indicate weight in kg and albumin in g/L
## equivalent dose for an exposure produced by a typical 750 mg/m² dose
## to a 1.73m² patient (70kg, 160cm)
```

This code can be copied-pasted directly on the R prompt, then use the "CPDOSE" function as, for example :

```
CPDOSE(weight=70, albumin=40, typical.dose=750) ##typical patient, 70kg, 40g/L
CPDOSE(weight=41, albumin=19, typical.dose=750) ## cachectic patient
CPDOSE(weight=112, albumin=47, typical.dose=750) ## overweight, hyperalbuminemia
```

The code can also be copied in a text editor and saved in a "CP_dosing.R" file. Then drag and drop the file on the R prompt and write the CPDOSE(...) function at the prompt as above.

Appendix. Figure: The CPDOSE function is written or copied at the prompt, with specific « weight » and « albuminemia » arguments. Thereafter, the function returns a two-row table. The 1st row gives the dose and exposure for the typical patient (70 kg and 40 g/L albumin, corresponding 1.73 m^2) and the 2nd line gives the dose recommendation for the specific patient. The « typica.dose » argument may be changed if a different exposure is targeted. The three examples show the results for the typical patient, a cachectic patient and the same cachectic patient for which a greater exposure (corresponding to 400 mg/m^2) is targeted.



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