Characterization of Cyclophosphamide Pharmacokinetics and Its Age-Appropriate Dosing Strategy in Children and Adolescents through Population Pharmacokinetic Modeling

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Directed by Professor Chuhl Joo Lyu

A Doctoral Dissertation
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Medical Science

Jung Woo Han

December 2023

This certifies that the Doctoral Dissertation of
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ACKNOWLEDGMENTS

The outcome of this study required much guidance and inspiration from Professor Chuhl Joo Lyu. I would like to deeply thank him for all of his support and encouragement throughout the completion of this study.

I also especially express my gratitude to Professor Sung Young Rha for teaching and guiding me to start, move on, and complete the professional education journey to master medical oncology.

I owe my profound gratitude to Professor Kyungsoo Park, and Dongwoo Chae for guiding me to understand the basic principles of population pharmacokinetics and to start and accomplish all the processes during the model developments and refinements. I also would like to thank you Dr. Hyun Soo Park for supporting the initial start of this study and the model development.

I would like to express my gratitude to Professor Sang-Guk Lee of the Department of Laboratory Medicine for setting up and providing the laboratory measurement of cyclophosphamide drug concentration.

I also want to show gratitude to Professor Jae Min Lee who gave me insight on the enthusiastic research efforts and always supported and guided me to complete this study.

Finally, I would like to give special thanks to Professor Joohyuk Sohn, Gun Min Kim, Min Hwan Kim, Ji Eun Jang, and Seung Min Hahn for showing great interest and appreciate the value of the research and

making an effort to enroll the patients. Also, I thank all my colleagues in the Department of Pediatric Hematology and Oncology, and the Department of Pediatrics for overcoming the challenges that we have never experienced before.

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ABSTRACT

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The cytotoxic chemotherapy is still the mainstay for cancer treatment, however, the regimen and dose have been empirically adjusted for age and performance status. Moreover, the regimen for adolescents and young adults has not been developed because of the lack of evidence. In this study, we aimed to suggest age appropriate dosing regimen by the population pharmacokinetics study of cyclophosphamide.

A total of 32 children, adolescents, and young adults receiving cyclophosphamide-containing regimens in clinical practice were included in this study. The sampling was prospectively collected according to predefined timing. The population pharmacokinetics modeling was performed and the individual regimens were simulated using Monolix suite 2021R2.

A two-compartment model with first-order elimination best described the dataset. For an individual with a body weight of 28.3kg, 10 years of age, and a body surface area of 1.0 m^2, the typical values of estimated central and peripheral volume of distribution, clearance, and intercompartmental clearance were 6553.6 mL, 6661.3 mL, 2828.9 mL/h, and 4932.1 mL/h, respectively. In the simulation, maximal concentration (Cmax) and Area under the

curve (AUC) decreased until 10 years old and increased thereafter to 20 years old with a body surface area-based dosing regimen. To match the Cmax and AUC to 10 years old age using BSA based regimen, the dose should be reduced to 95% dose for 180mins in 3 years old group and 70% dose for 80 mins in 20 years old group, from 1200 mg/m^2 cyclophosphamide dose for 3 hours infusion in typical standard body size 10 years old group, respectively.

The population pharmacokinetic model of cyclophosphamide was developed properly, and an appropriate regimen for the specific age group was suggested. Further refinement and validation of the model would enhance the background of age-appropriate, model-based dosing adjustment for cancer patients across various age groups

Keywords: population pharmacokinetics, children, adolescents, cyclophosphamide

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I. INTRODUCTION

In recent years, the field of cancer treatment has made remarkable progress with the development of various groundbreaking anti-cancer therapies such as molecularly targeted therapies and immuno-oncology[1,2]. Discoveries in the biology of cancer itself have also been an important area of advancement in oncology, leading to remarkable improvements in cancer survival rates compared to decades ago[1,2]. Nevertheless, cytotoxic chemotherapy remains the mainstay of treatment for many cancers[3,4]. How to appropriately use cytotoxic chemotherapy is an important topic in the field of oncology, but it is still limited to treating patients with simple body surface area or weight-based dosing calculations.

Age-appropriate use of cytotoxic chemotherapy is a critical topic for improving survival. It was well-recognized 20 years ago that when treating the same group of adolescent and young adult patients, there are differences in survival according to how cytotoxic anticancer

therapies are used[5]. In 2008, a comparison of clinical trials in the Children's cancer group and Cancer and Leukemia group B on the same group of adolescent patients with acute lymphoblastic leukemia revealed a striking finding: the survival rate of patients treated with the CCG's regimen was more than twice as high as that of patients treated with CALGB's regimen[6]. The main difference between the two regimens was the use of cytotoxic chemotherapy, with significant differences in the dose and duration of non-myelosuppressive agents[6]. The CALGB regimen was based on a clinical trial in adults, while the CCG regimen was based on a clinical trial in children, meaning that the best regimen for the same acute lymphoblastic leukemia should be different for different age groups.

Presumably, these age-related differences in chemotherapy response are not unique to leukemia. When tumors that appear in adults, such as colon, stomach, and breast cancer, appear in children, or when childhood cancers, such as rhabdomyosarcoma and Ewing's sarcoma, appear in adults, it is hard to imagine that a chemotherapy regimen designed for one age group would have the same therapeutic outcome when applied to another[7]. It is well known that survival rates for rhabdomyosarcoma, Ewing's sarcoma, and other cancers decline with age, and while this may be due to the biology of the tumor, it may also be because the appropriate use of chemotherapy has not been established for different age groups[8-10].

While pediatric and adult survival rates have improved significantly over the past few decades due to the development of appropriate therapies, this improvement has been slower in adolescents, a phenomenon known as the AYA gap[11]. The field of Adolescent and Young Adult Oncology (AYAO) has emerged to overcome this lack of survival improvement. Although the age of AYA is difficult to define and there are conflicting opinions among experts, the consensus is that the age of AYA is approximately 15-40 years old, to allow for more comprehensive research and development of treatment regimens[12]. Tumors seen in AYA can be both pediatric and adult cancers, and cancers that are more specific to AYA include sarcomas, germ cell tumors, thyroid cancer, and breast cancer[13]. Although it is easy

to assume that one size does not fit all, age-specific cytotoxic chemotherapy has still not been extensively developed.

To address the stagnation in improving cancer survival rates among adolescents and young adults (AYA), it's crucial to first examine how age-specific differences affect the pharmacokinetics of prevalent cytotoxic chemotherapy drugs. In general, fat mass and fat-free mass change as a child progresses to adulthood. Specifically, it's observed that older adults, particularly those in their 60s and beyond, exhibit increased body fat, reduced plasma volume, diminished total body water, and a decrease in extracellular body fluid, in contrast to those in their 20s[14,15]. As the maturation and aging of the liver and kidneys differ in metabolic pathways, the main metabolic pathway of the same drug changes with age[16,17]. Given the long history of cytotoxic chemotherapy, one would expect to see a lot of results on age-related characteristics in pharmacokinetics and the development of proper regimens considering age, however, such data is still very scarce. Most studies have only been done in children alone or adults alone, and very few have compared the two groups[18].

Compared to traditional pharmacokinetics, which explores population-averaged pharmacokinetic parameters in a very narrowly selected patient population, population pharmacokinetics provides valid pharmacokinetic information in an appropriate patient population that is representative of the patient population to be treated and allows for the construction of models that recognize and quantitatively interpret interindividual, intraindividual, and interoccurrence variability[19]. In addition, various demographic, pathophysiological, environmental, or drug-related covariates can be included in the model to explain the pharmacokinetic properties of the drug[19]. In particular, it can be applied in cases where the number of concentration samples is small or the variation is high, and it can be applied in cases that are difficult to study in traditional ways, such as neonates, the elderly, or rare diseases[19]. It can be used to calculate appropriate drug doses in phase 2 and 3 studies or to suggest individualized doses to achieve appropriate pharmacodynamic effects in real-world clinical practice[20].

In this study, we studied cyclophosphamide pharmacokinetic parameters, one of the most commonly used cytotoxic chemotherapy for various cancers, across the entire age range from children to young adults. We built a model using population pharmacokinetic methodology to provide baseline information for developing age-specific anticancer cytotoxic chemotherapy regimens from children, adolescents, and young adults.

II. MATERIALS AND METHODS

1. Subjects

A total of 32 children and adolescent patients with cancer from 0 to 25 years old who were treated with a cyclophosphamide-containing regimen were enrolled in this study. The age groups were divided into 5 groups by 5 years, and the maximum number enrolled in each group does not exceed 5. The representative regimens included VAC (vincristine, actinomycin, cyclophosphamide), VDC (vincristine, doxorubicin, cyclophosphamide), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), AC (doxorubicin, cyclophosphamide), et Cetra (Table 1). Other regimens also were allowed at the description of investigators, before the patient enrollment. The inclusion criteria for this study were at least 7 days after the previous chemotherapy regimen should be elapsed, all subjects should have normal organ function defined as creatinine level less than 2 upper normal limits for age, alanine aminotransferase/aspartate aminotransferase less than 5 upper normal limits for age, total bilirubin and direct bilirubin less than 3 times of upper normal limit for age, and serum albumin over 2.0 g/dL. The enrolled patient dosing records for the chemotherapeutic regimen were collected.

Table 1. The representative regimen for this study used for cyclophosphamide concentrations

No	Regimen	Dose
1	A1101 regimen	Vincristine 1.5mg/m^2 Cyclophosphamide 250mg/m^2 D1, D2, D3 5FU 400mg/m^2 Etoposide 150mg/m^2 for 3 hours D1
2	M051 Regimen, (1st~8th cycle)	Cisplatin 75mg/m^2 D1

		Vincristine 1.5mg/m^2 Cyclophosphamide 1000mg/m^2 D2, D3
3	M051 Regimen (9th~12th cycle)	Vincristine 1.5mg/m^2 Cyclophosphamide 1000mg/m^2 for 3 hours (D1~D2)
4	S081A Regimen	Vincristine 1.5mg/m^2 Etoposide 75mg/m^2 for 3 hours D1, D2, D3 Cisplatin 90mg/m^2 for 6 hours D1 Cyclophosphamide 1500mg/m^2 for 3 hours D2, D3
5	G082B Regimen	Bleomycin 15mg/m^2 for 30 mins D3 Etoposide 150mg/m^2 for 3 hours D1, D2, D3 Cyclophosphamide 2000mg/m^2 for 3 hours D1, D2, D3
6	S1101 A Regimen (PNET, ATRT)	Vincristine 1.5mg/m^2 Cyclophosphamide 1000mg/m^2 for 3 hours D2, D3 Etoposide 75mg/m^2 D1, D2, D3 Cisplatin 60mg/m2 D1
7	AC chemotherapy	Doxorubicin 60mg/m^2 IV shooting (5mins) Cyclophosphamide 600mg/m^2 IV shooting (5mins)
8	High risk consolidation	Cyclophosphamide 1000mg/m^2 for 3 hours
9	High risk consolidation	Cyclophosphamide 1000mg/m^2 for 3 hours
10	High risk intensification	Vincristine 1.5mg/m^2 D1, D8, D15 Doxorubicin 25mg/m^2 for 30 mins D1, D8, D15 L-asparaginase (E. coli or Pegylated form)

		Dexamethasone 10mg/m^2 sig PO
11	High risk intensification	Cyclophosphamide 100mg/m^2 for 3 hours (D1)
12	Standard risk consolidation	Cyclophosphamide 1000mg/m^2 for 3 hours
13	Standard risk intensification	Vincristine 1.5mg/m^2 D1, D8, D15 Doxorubicin 25mg/m^2 for 30 mins D1, D8, D15
14	CHOP	Vincristine 1.4mg/m^2 Cyclophosphamide 750mg/m^2 IV shooting or infusion for 1 hour Doxorubicin 50mg/m^2 IV shooting or infusion for 1 hour Prednisolone 100mg D1~5
15	Hyper-CVAD-A	Cyclophosphamide 300mg/m^2 B.I.D. Vincristine 1.4mg/m^2 D4, D11 Doxorubicin 25mg/m^2 D4, D5 Dexamethasone 40mg D1~4, D11~14
16	VIDE	Vincristine 1.5mg/m^2 D1 Doxorubicin 20mg/m^2 for 30mins D1, D2, D3 Etoposide 100mg/m^2 for 3 hours D1, D2, D3 Ifosfamide 3000mg/m^2 for 3 hours, D1, D2, D3
17	CAV	VCR 0.67mg/m^2 Doxorubicin 25mg/m^2 for 3 hours Cyclophosphamide 2100mg/m^2 for 6 hours
18	CD chemo	Cisplatin 120mg/m^2 for 4 hours D1 Doxorubicin 25mg/m^2 for 8 hours D1, D2, D3
19	CD chemo2	Cisplatin 60mg/m^2 for 4 hours D1, D2

		Doxorubicin 25mg/m^2 for 8 hours D1, D2, D3
20	VDC1	Vincristine 1.5mg Cyclophosphamide 1200mg/m^2 for 30mins Doxorubicin 37.5mg/m^2 for 24 hours
21	VDC2	Vincristine 1.5mg/m^2 D1 Doxorubicin 37.5mg/m^2 for 24 hours D1, D2 Cyclophosphamide 1200mg/m^2 for 30 mins D1
22	VDC3	Vincristine 1.5mg/m^2 Doxorubicin 50mg/m^2 for 30mins D1 Cyclophosphamide 1000mg/m^2 for 3 hours D1
23	VAC1	Vincristine 1.5mg/m^2 Actinomycin-D 0.45mg/m^2 D1~D5 Cyclophosphamide 1,500mg/m^2 D1
24	AI	Doxorubicin 25mg/m^2 for 30 mins D1, D2, D3 Ifosfamide 2500mg/m^2 for 3 hours D1, D2, D3

This study was approved by the institutional review board of Severance Hospital (IRB approval No. 4-2018-0419) and performed following the regulatory requirements including the Declaration of Helsinki and the Good Clinical Practice.

2. Blood sampling and cyclophosphamide assay

Subjects were administered with cyclophosphamide under a routine cancer chemotherapy practice schedule without any modification. Sampling times were scheduled at the pre-dose, peak(10 mins), 2 hours, 5 hours, 12 hours, and 24 hours and adjusted to the regimen. The scheduled sampling times were described (Table 2). Blood sampling was drawn through the chemoport, Hickmann catheter, or heparin lock. Predose sampling was

omitted when the previous cyclophosphamide was administered at least 7 days ago. The sampling time window was allowed ± 30 minutes except for the peak sampling timing. Plasma 20 μL was mixed with 1μg/mL of internal standard (CYP-d4) in 80 μL of acetonitrile. The mixture was centrifuged at 14,000 RPM, room temperature for 10 mins. Subsequently, 10 μL of the supernatant was combined with 990 μL of mobile phase A, and this mixture was vortexed for 30 secs. The mixture was further diluted into 1000X. The cyclophosphamide concentration was analyzed with LC-MS(Liquid chromatography–mass spectrometry system, AB SCIEX QTRAP 5500 coupled with Agilent 1290 infinityII) and column (Imtakt Unison UK-C18). The concentration was expressed as μg /mL.

Table 2. Proposed sampling time for population pharmacokinetics study

infusion duration	Pre-Dose	Peak	T1	T2	T3	Trough
IV shooting	0	10min	2HR	5HR	12HR	24HR
30 mins	0	40min	2HR	5HR	12HR	24HR
3 hours	0	3HR 10min	5HR	8HR	12HR	24HR
6 hours	0	6HR 10min	7HR	9HR	12HR	24HR

3. Population PK modeling

Within the context of a mixed effect model framework, a model parameter was defined as follows:

$$P_i = \theta \cdot \exp(\eta_i)$$

Here, P_i represents the parameter value for the *i*th individual, θ signifies the typical value of the parameter, and η_i denotes a random difference between individuals, which is assumed to follow a Gaussian distribution with a mean of zero and a variance of ω^2. To account for residual variability, three types of error models were considered: additive, proportional, and a combined approach and the combined error model was formulated as:

$$Y_{ij} = PRED_{ij} \cdot \left(1 + \varepsilon_{pro_{ij}}\right) + \varepsilon_{add_{ij}}$$

In the combined error model, the observed and predicted concentrations for individual *i* at time point *j* are presented by Y_{ij} and $PRED_{ij}$ respectively. The terms $\varepsilon_{pro_{ij}}$and $\varepsilon_{add_{ij}}$ denote the proportional and additive residual errors. These errors are assumed to be normally distributed with a mean of zero, capturing the discrepancy between observed and predicted values in the model.

The plasma concentrations of cyclophosphamide were analyzed using a mammillary compartment pharmacokinetic (PK) model. In this model, the elimination of the drug was presumed to adhere to first-order kinetics. To accurately describe the distribution of cyclophosphamide within the body, the model explored variations with one, two, or three compartments, testing each to determine the most suitable representation of the drug's disposition.

4. Covariate analysis

Using allometry based on the body weight (WT), the body surface area (BSA), typical volume, and clearance parameters were described by the following equation :

$$\theta = \lambda_{pop} * (\frac{WT}{median\ WT})^{\beta_{wt}}$$

$$\theta = \lambda_{pop} * (\frac{BSA}{median\ BSA})^{\beta_{bsa}}$$

In the given formula, λ_{pop} represents the parameter value for an individual subject. The β_{wt} and β_{bsa} are the allometric exponent for WT and body mass index (BMI), respectively. During the process of model exploration, these exponents, the β_{wt} and β_{bsa} were either estimated or assigned fixed values. When the β_{wt} was fixed, 1 and 0.75 were chosen for volume and clearance parameters, respectively.

Continuous variables such as age (AGE), BMI, and height (HT) were also explored. After exploration of the age effect on the parameters, the piecemeal variable of minAgeMedian which was defined as max(0, AGE-medianAge years old) was selected for

the covariate. The BMI and HT with allometric scaling were also tested for the covariate effect on the PK parameters. Preliminary covariate explorations were done by linear regression of covariates on the estimates of individual parameters using R. A systematic covariate exploration was conducted using a stepwise covariate model-building approach, which was guided by the likelihood ratio test. This method adhered to specific selection criteria: $p < 0.05$ for forward addition (ΔOFV 3.84) and $p < 0.01$ (ΔOFV 6.6) for backward elimination. For continuous covariates, both linear and exponential functions were tested, while for categorical covariates, the relationships were assessed using linear functions.

5. Model evaluation

Employing the finalized pharmacokinetic model, its adequacy was evaluated through a series of indices: goodness-of-fit diagnostics, model stability, precision of parameters, and the visual predictive check (VPC). The VPC involved the use of 1000 simulated datasets, which were utilized to juxtapose the model's predictions against the actual observed data. This comparison provided a visual assessment of how well the model could predict the observed concentrations.

6. Simulation

The finalized model was applied to simulate two key pharmacokinetic profiles: the concentration-time curve and the area under the curve (AUC) in subjects who received a conventional dose of cyclophosphamide. This dose was administered based on BSA or per kilogram (Kg) of BW; (i) a single dose of 1200 mg/BSA, (ii) a single dose of 40 mg/kg, to explore the variability of Cmax and AUC between the typical patients. Typical patients were selected for the representative age and body size. Body size represented standard, big, and obese. The typical ages were selected as 3, 5, 10, 12, 15, and 20 years to represent babies, children, adolescents, and young adults. The subject with standard body size represented the average (50 percentile) of body size specific to the age. The subject with a big body size represented over 95 percentile of body size specific to the age. The subjects

with obesity represented the same BSA as big subjects, however, BMI was over the criteria for obesity specific to the age (Table 3). All subjects were regarded as male because there was no variation according to sex.

Table 3. Age and body size group to represent the typical patient group to simulate the dosing effect

Age Group	Size Group	Height (cm)	Weight (kg)	BSA (m^2)	BMI (kg/m^2)	40 mg per kg	1200 mg per BSA
3	Standard	96	15.0	0.6325	16.3	600	759
3	Big	103	17.0	0.6974	16.0	680	837
3	Obese	97.3	18.0	0.6975	19.0	720	837
5	Standard	110	19.0	0.7619	15.7	760	914
5	Big	118	24.5	0.8961	17.6	980	1075
5	Obese	112	25.8	0.8959	20.6	1032	1075
10	Standard	139	35.0	1.1625	18.1	1400	1395
10	Big	150	50.5	1.4506	22.4	2020	1741
10	Obese	142	53.3	1.4500	26.4	2132	1740
12	Standard	152	45.0	1.3784	19.5	1800	1654
12	Big	163	63.0	1.6889	23.7	2520	2027
12	Obese	156	65.8	1.6886	27.0	2632	2026
15	Standard	169	60.0	1.6783	21.0	2400	2014
15	Big	179	78.0	1.9693	24.3	3120	2363
15	Obese	171	81.6	1.9688	27.9	3264	2363
20	Standard	174	68.0	1.8129	22.5	2720	2175
20	Big	185	86.0	2.1022	25.1	3440	2523
20	Obese	176	90.4	2.1023	29.2	3616	2523

Acronyms and Abbreviations; BMI, body mass index, BSA, body surface area;

For simulation, 100 replicates of the dataset were generated, each being sampled according to the representative subjects (a total of 12 groups). The median and 90% prediction intervals of the simulated cyclophosphamide concentrations or AUC–time profiles were calculated for different patient groups and dosing regimens (BSA-based dosing and weight-based dosing). The concentration and AUC were compared among the patient groups receiving BSA-based dosing or weight-based dosing.

Software

Data analysis and output evaluations were performed using Monolix and Simulx 2021R2 (Lixoft SAS, a Simulations Plus company). All analyses and generation of graphs were performed by using R Statistical Software (v4.3.1; R Core Team 2023)

III. RESULTS

1. Subjects

A total of 32 children and adults with cancer were included in this study. Out of these participants, 20 were male. The median age of the subjects in the group was 9.8 (range, 1.7 – 20.8) years old. The median WT was 35.2 (range 10.0 – 65.0) Kg, and the median BSA was 1.2 (0.5 – 1.8) m^2. The most common diagnosis was brain tumor (n=18, 56.2%), rhabdomyosarcoma (n=3, 9.4%), and neuroblastoma (n=3, 9.4%). Organ function represented with kidney, and liver functions were all within normal range (Table 4).

Table 4. Demographic findings of the included patients

characteristics		value
gender (n, %)		
	F	12 (37.5%)
	M	20 (62.5%)
diagnosis (n, %)		
	brain tumor	18 (56.2%)
	neuroblastoma	3 (9.4%)
	rhabdomyosarcoma	3 (9.4%)
	acute lymphoblastic leukemia	1 (3.6%)
	clear cell sarcoma of the kidney	1 (3.6%)
	Hodgkin lymphoma	1 (3.6%)
	medulloblastoma	1 (3.6%)
	non-Hodgkin lymphoma	1 (3.6%)
	retinoblastoma	1 (3.6%)
	spinal cord tumor	1 (3.6%)
	Wilms tumor	1 (3.6%)
age (years) (median, range)		9.8 (1.7 – 20.8)
age groups (n)		

	0~5 yo	11
	5~10 yo	6
	5~15 yo	9
	15~21 yo	6
body size (median, range)		
	height (cm)	140.5 (81.3 – 176)
	weight (kg)	35.2 (10 – 65)
	body surface area (m^2)	1.2 (0.5 – 1.8)
	body mass index (kg/m^2)	17.2 (14.1 – 23.2)
complete blood count (median, range)		
	white blood cells (/uL)	3725 (1510 – 8860)
	neutrophil (/uL)	2500 (860 – 7030)
	hemoglobin (g/dL)	9.1 (7.5 – 13.4)
	platelet (/uL)	225500 (50000 – 365000)
chemistry (median, range)		
	blood urea nitrogen (mg/dL)	8.2 (3 – 16.5)
	creatinine (mg/dL)	0.3 (0.1 – 0.8)
	aspartate aminotransferase (U/L)	29.5 (15 – 57)
	alanine aminotransferase (U/L)	19 (8 – 74)
	total bilirubin (mg/dL)	0.3 (0.1 – 0.9)
	total protein (g/dL)	6.5 (5.8 – 7.7)
	ablumin (g/dL)	4.4 (3.8 – 5)

2. Population PK modeling

A total of 200 samples were taken for plasma concentration of cyclophosphamide concentrations (12 subjects with 7 sampling points each, 16 subjects with 6 points, and 4 subjects with 5 points, each).

We examined one-, two-, and three-compartment disposition models, all incorporating first-order elimination, to best describe the pharmacokinetics of the drug in question. Ultimately, the two-compartment model emerged as the most accurate in characterizing our data, demonstrating good precision, as illustrated in Figure 1. In this selected model, interindividual variability was accounted for in several pharmacokinetic parameters: systemic clearance (Cl), central volume of distribution (Vc), peripheral volume of distribution (Vp), and inter-compartmental clearance (Q).

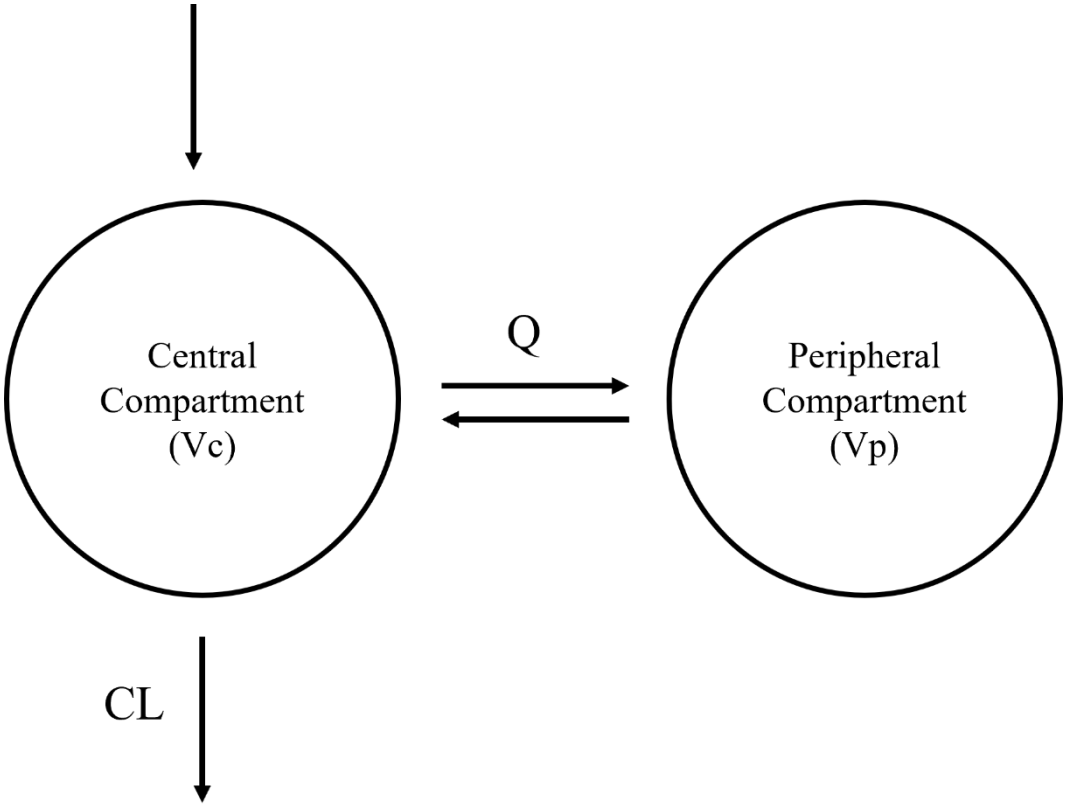


Figure 1. Schematic diagram of the structural model.
Q represents intercompartmental clearance between the central(Vc) and peripheral compartment(Vp).

3. Covariate analysis

In the first step, BW was added to Vc and Vp decreasing the objective function value (OFV) by 36.7 ($p<0.001$) from model 4 which were interindividual variability applied on all the parameters; Vc, Vp, CL, and Q of initial two compartmental model(model 6, Table 5). The Wt was added to model 6, and on the other hand, BSA was added to model 6 and both models showed significantly improved OFV(model 7 and model 9, Table 5). The β_{BSA} or $\beta_{Wt}$for CL was estimated, and The β_{wt} for Vc and Vp was fixed to 1. Then, in the next step, minAge10 was added to CL, and OFV was further decreased by 6.1 and 6.2, respectively ($p<0.05$) from model 7 and 9. No other parameter-covariate relationship was found to be significant (Table 5). Between Model 8 and Model 10, which were considered equivalent in terms of improvement in the OFV, Model 10 was selected as the final model.

Table 5. Model building process for cyclophosphamide pharmacokinetics

	Model description	Included covariates	Result	OFV	AIC	BIC	BICCc
1	Initial 1-compartment model		proper convergence	1896.2	1894.2	1900.1	1907.3
2	Initial 2-compartment model		proper convergence	1173.6	1185.6	1194.4	1205.3
3	Initial 3-compartment model		proper convergence	1195.1	1211.8	1237.8	1237.4

4	model 2 and BSV on Vc, Vp, CL		significantly improved OFV	1045.2	1063.2	1076.4	1087.3
5	model 4 and allometry effect of weight on Vc	Wt on Vc	significantly improved OFV and decreased variability (both BSV and RUV)	1023.6	1041.6	1054.8	1065.7
6	model 5 and allometry effect of weight on Vp	Wt on Vc, Vp	significantly improved OFV and decreased variability (both BSV and RUV)	1008.5	1026.5	1039.7	1050.6
7	model 6 and allometry effect of weight on CL	Wt on CL, Vc, Vp	significantly improved OFV from model 6	971.0	991.0	1055.7	1016.6
8	model 7 and minage10 linear model in CL	Wt on CL, Vc, Vp; Age on CL	significantly improved OFV and increased variability (both BSV and RUV)	964.9	986.9	1003.1	1014.0

9	model 6 and allometry effect of body surface area on CL	BSA on CL; Wt on Vc, Vp	significantly improved OFV from model 6	971.3	991.3	1006.0	1016.9
10	model 9 and minage10 linear model in CL	BSA on CL; Wt on Vc, Vp; Age on CL	significantly improved OFV and decreased variability (both BSV and RUV)	965.4	987.4	1003.5	1014.4

AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; BICCc, Corrected BIC; BSV, between subject variability; -2LL, -2 log-liklyhood; OFV, objective function value; RUV, residual unknown variability;

The analysis involving a plot of covariates versus individual parameters revealed the correlations. Specifically, a relationship between age or BSA and clearance was evident, as well as a correlation between WT and the central volume or peripheral volume. As a result of these observed correlations, the covariates of age, WT, and BSA were deemed significant and were consequently incorporated into the model (Fig 2).

The plot of covariates and or etas of the model before the addition of age as a covariate to the model and the final model, age showed the systematic correlation with clearance. After age as a covariate was added to the model, the correlation disappeared and therefore, the final model was accepted (Fig 3).

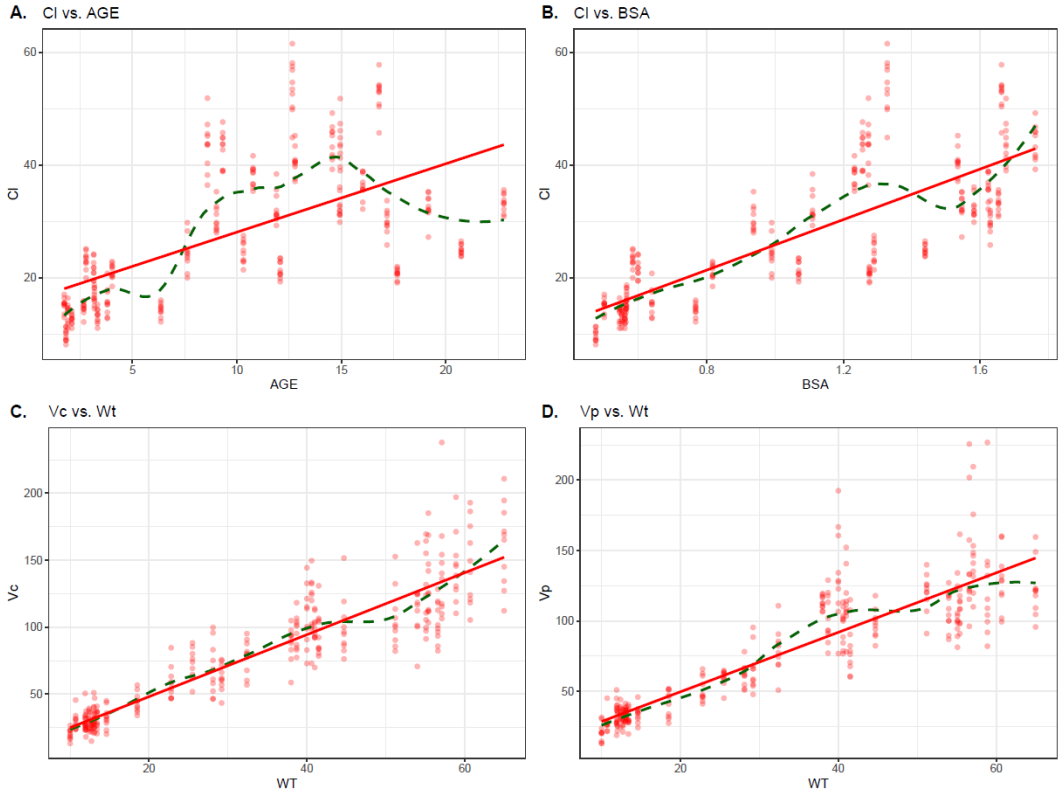


Figure 2. Representative plots for individual parameters vs. covariates.

(A) clearance vs. age, (B) clearance vs. body surface area, (C) central volume vs. body weight, and (D) peripheral volume vs. body weight. The red solid line represents the linear regression line, and the dark green dashed line represents the loess spline curve. (BMI, body mass index; Cl, clearance; WT, body weight; Vc, central volume)

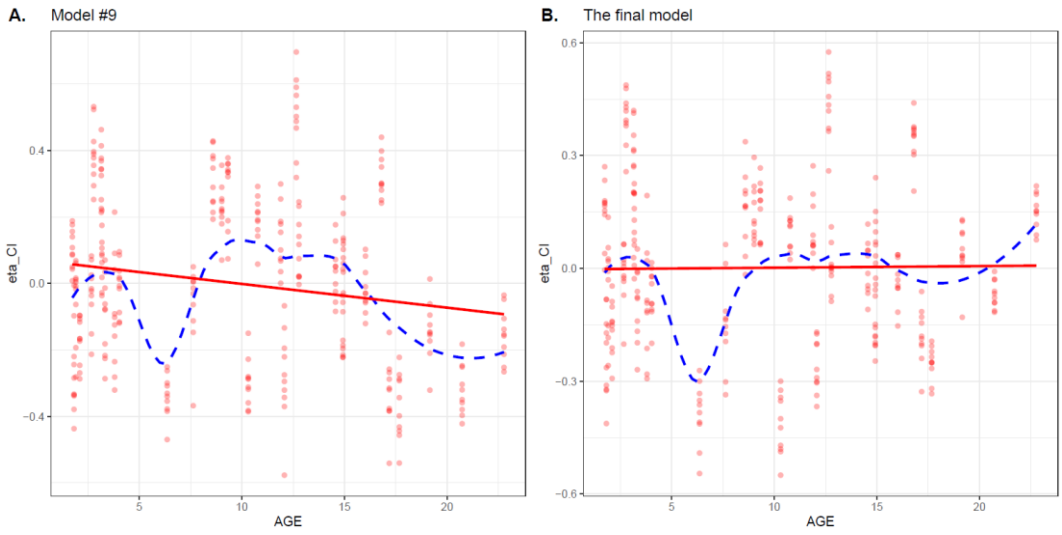


Figure 3. Eta of clearance versus age plot.

(A) model 9 (applied covariate of weight on central volume and peripheral volume, and body surface area on clearance) (B) the final model. Systematic correlation disappeared when the covariate of age was applied to clearance for the final model. The red solid line represents the linear regression line, and the dark green dashed line represents the loess spline curve.

4. Final model parameter estimates

For individuals with WT of 28.3kg, 10 years of age, and BSA of 1.00 (m^2), the CL was 2828.9 mL/h, Vc was 6553.6 mL, Vp was 6661.3 mL and Q was 4932.1 mL/h, respectively (Table 6)

Given these results, typical values of CL, Vc, Vp, and Q, denoted as TVCL, TVVc, TVVp, and TVQ, are expressed in the equations below:

1. TVCL (mL/hr) = $2828.9 \times \left(\frac{BSA}{1.002}\right)^{1.12} \times e^{(-0.043 * (\min(0, AGE-10)))}$
2. TVVc (mL) = $6553.6 \times \left(\frac{BWT}{28.309}\right)^{1}$

3. TVVp (mL) = 6661.3 $\times\left(\frac{BWT}{28.309}\right)^{1}$
4. TVQ (mL/hr) = 4932.1

Table 6. Population estimation for the final model

Structural parameters	Estimate	RSE(%)
CL (mL/h)	2828.87	6.45
log βCL_BSA	1.12	12.1
log βCL_minage10	-0.043	38.2
Vc (mL)	6553.55	19.1
log βVc_WT	1 (FIXED)	
Q (mL/h)	4932.08	24.6
Vp (mL)	6661.3	11.7
log βVp_WT	1 (FIXED)	
Inter-individual variabilities		
ω_CL	0.22	15.4
ω_Vc	0.23	45.6
ω_Vp	0.22	39.5
Error model parameters		
a_additive	0.4	18.9
b_proportional	0.2	11.2

β, exponent for effect; BMI, body mass index; CL, clearance; Q, intercompartmental clearance; minage10, max(0, AGE-10 years old); RSE, relative standard error; Vc, central volume; Vp, peripheral volume; WT, weight;

5. Model evaluation

The goodness of fit plots indicated a good agreement between the model-predicted concentrations and the actual observations over time (Fig. 4). Also, both the population and individual predictions were evenly distributed around the line of identity. This distribution is indicative of a good fit of the model (Fig. 5).

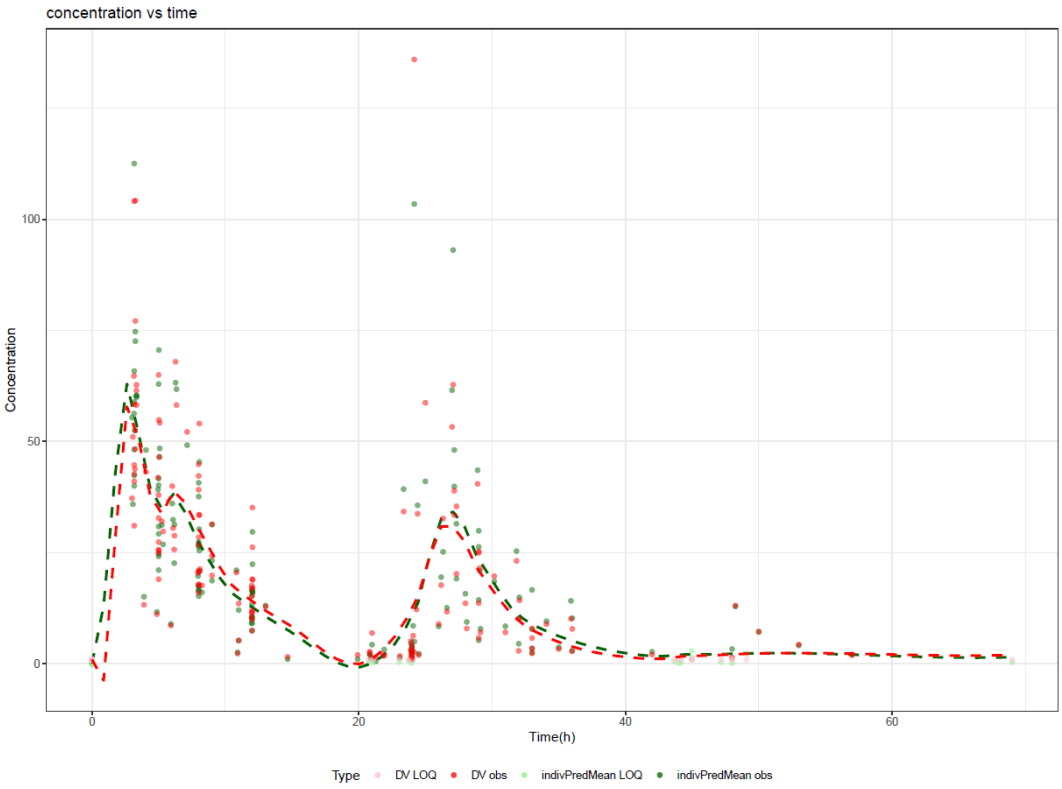


Figure 4. Goodness of fit plots of the population pharmacokinetics model of cyclophosphamide.

This represents the predicted concentrations and observation vs time. The red dots indicate observed data points, while dark green dots denote model predictions. The red dashed line illustrates the loess spline curve fitted to the observations, and the dark green dashed line corresponds to the loess spline curve fitted to the predictions.

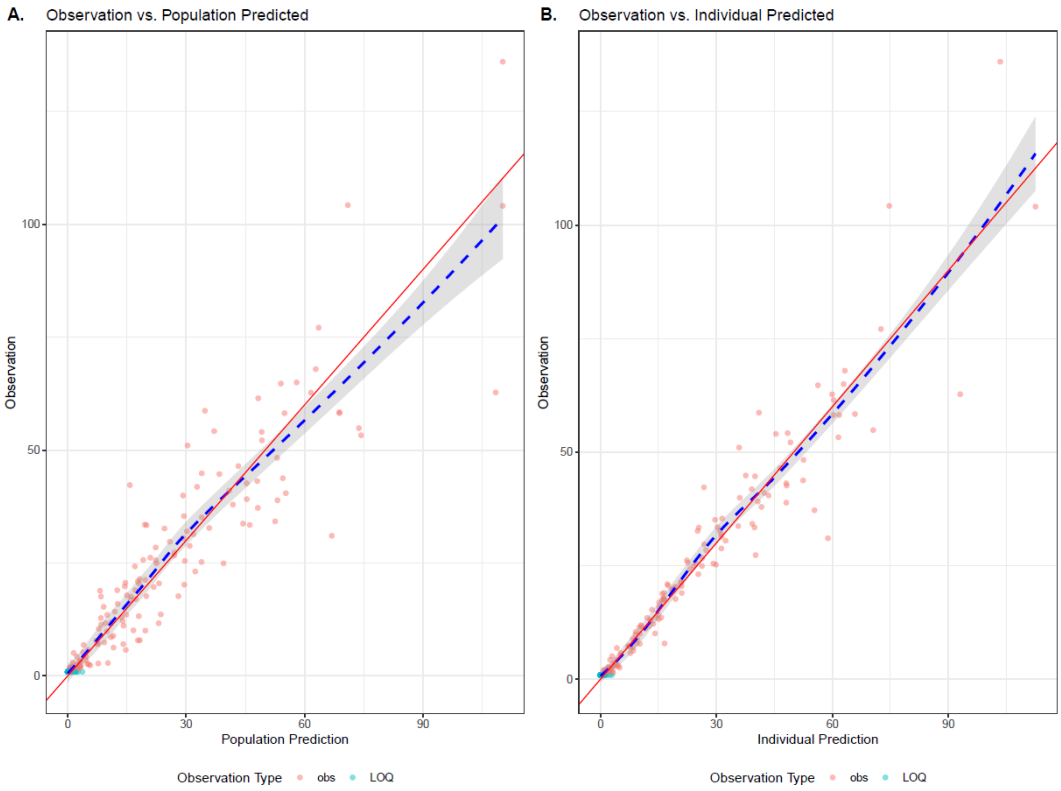


Figure 5. Goodness of fit plots of the population pharmacokinetics model of cyclophosphamide.

(A) observation vs. population prediction, (B) observation vs. individual prediction. The red dots indicate observations. The sky blue dots denote the limit of quantitation. The blue dashed lines represent the loess spline curve.

The plot of the individual weighted residuals showed the symmetrical distribution of the residuals around the line of zero and did not present an obvious trend. This indicated no evidence of model misspecification (Fig 6).

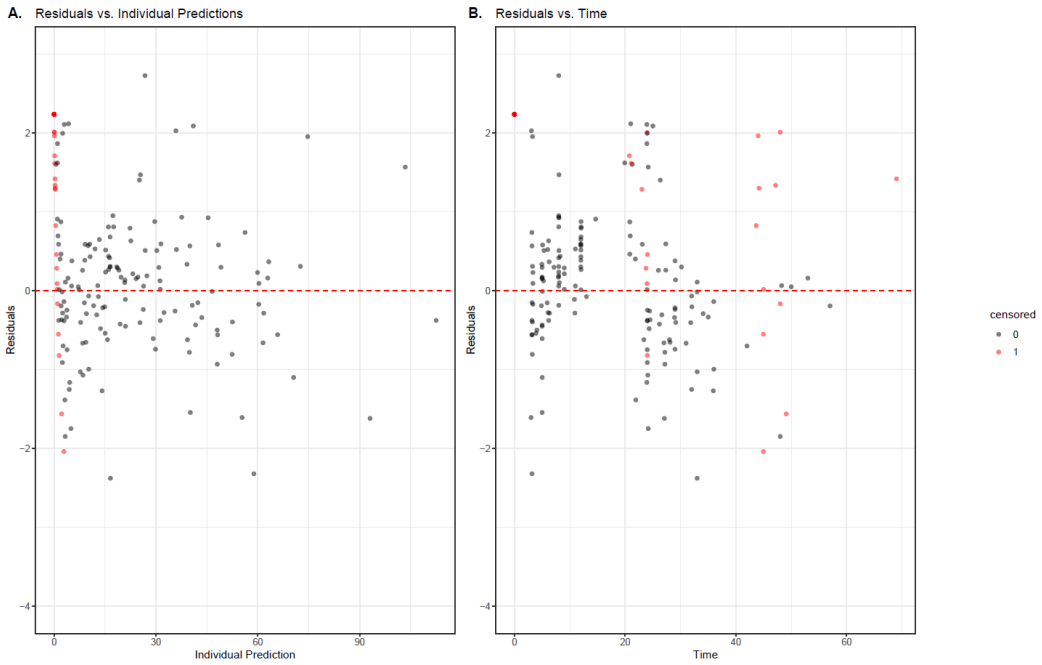


Figure 6. The residual plots of the population pharmacokinetics model of cyclophosphamide.

(A) individual weighted residual versus individual prediction, (B) individual weighted residuals versus time. The black dots showed the observations and the red dots indicated the limit of quantitation.

The overall evaluation of the goodness-of-fit suggested an absence of any apparent systematic bias in both the structural model and the residual error models. VPC plots revealed that the majority of the observed data points were encompassed within the 90% prediction interval of the simulated data, indicating the adequate predictive performance of the model (Fig. 7). From these results, we can conclude that our model performs well in predicting the cyclophosphamide concentrations.

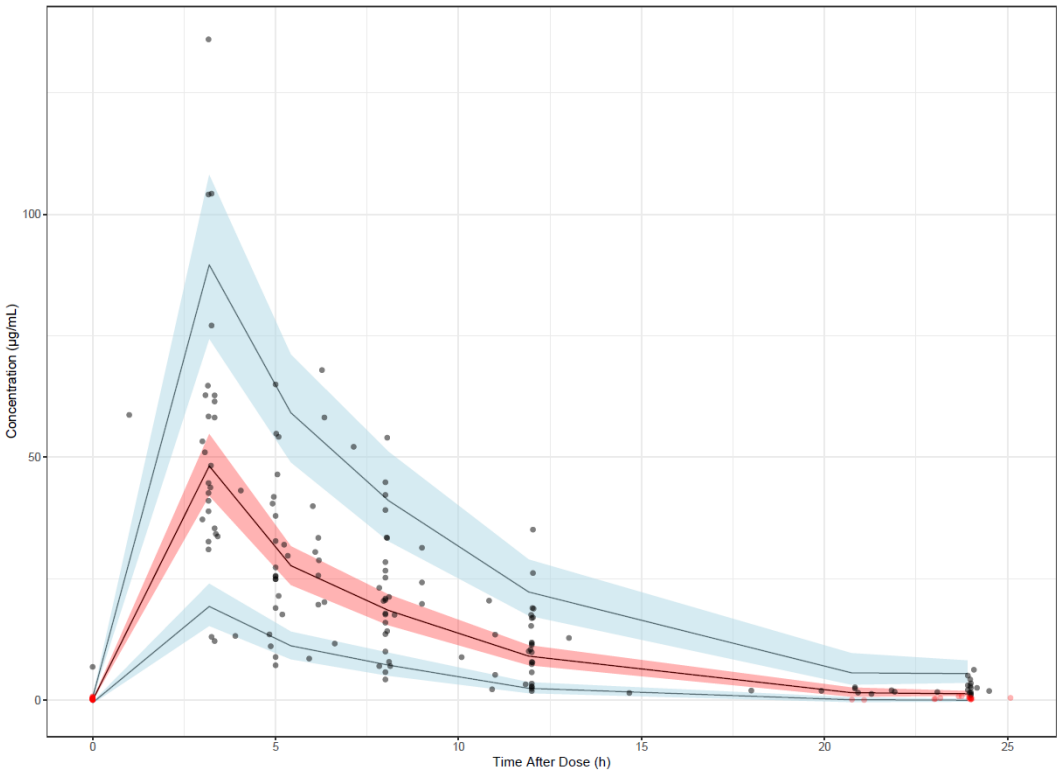
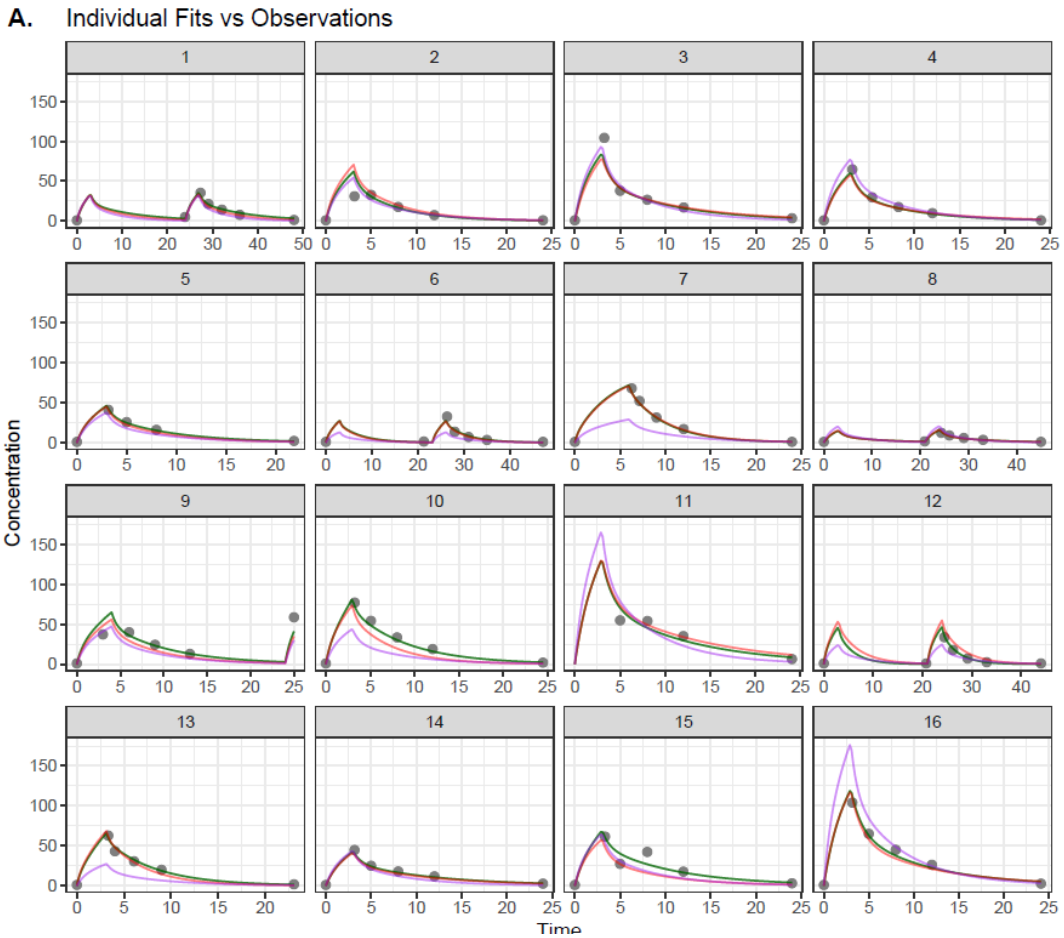


Figure 7. The visual predictive checks of the population pharmacokinetics model of cyclophosphamide.

The 3 lines in the figures represent observed percentile curves (upper solid line: 90 percentile, middle solid line: 50 percentile, and lower solid line: 10 percentile). The blue bands denote a 90% confidence interval of prediction (upper band, 90 percentile; lower band: 10 percentile of prediction). The black dots represent observed data and the red dots show censored data. All lines are well within their corresponding predictive bands of 90% confidence interval acquired after 1,000 simulations.

With the plots of all the individual fits, observation and prediction for each individual were in good agreement (Fig. 8).



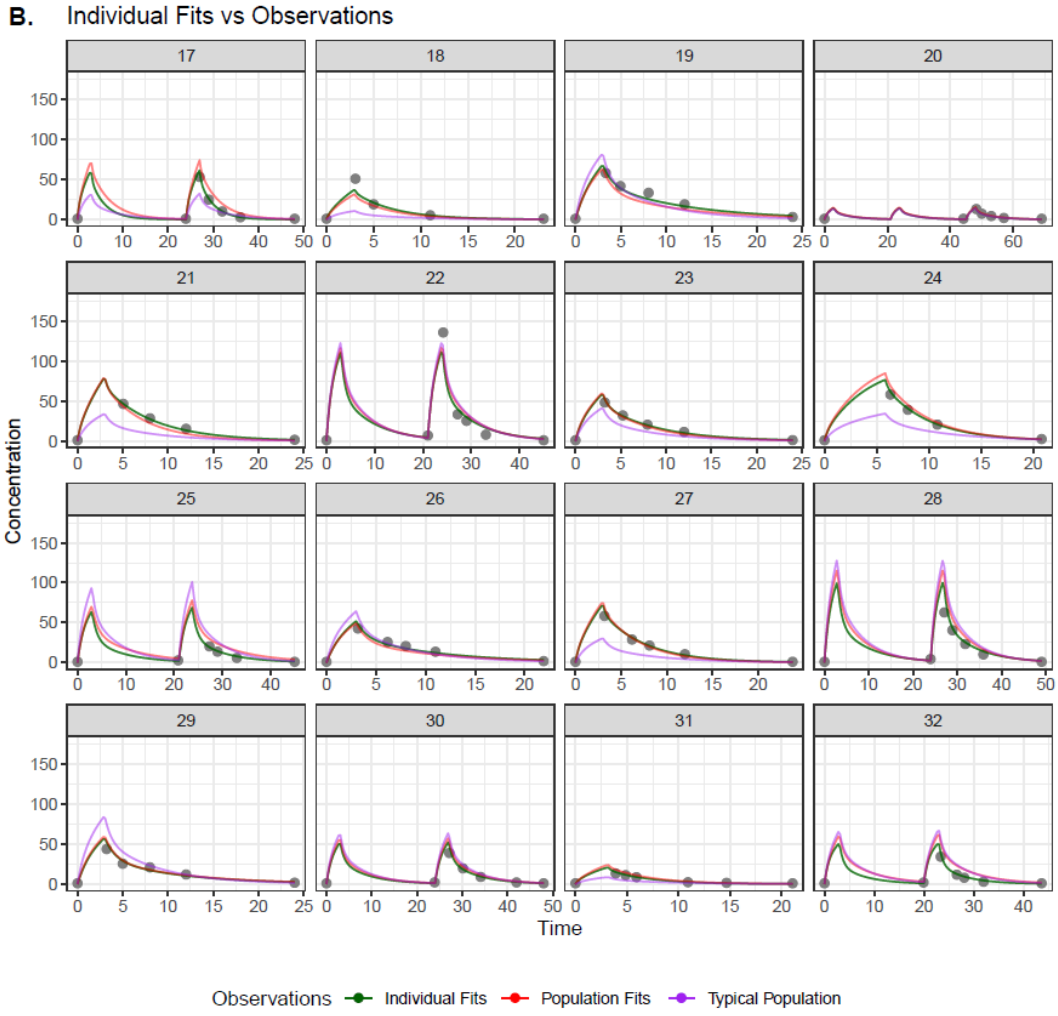


Figure 8. Individual fits, population fits using individual covariates, and population fits of typical individuals.

6. Simulation

We performed 1800 simulated patients (= 100 datasets x 18 patient groups/dataset) for each BSA and Kg-based cyclophosphamide dosing regimen. For the BSA-based regimen,

1200mg/BSA was administered and for the Kg-based regimen, 40mg/Kg was administered because the two regimens were considered equivalent in the clinical practice.

7. Body Surface Area (BSA) based dosing regimen

With the increased age for the same body size(standard, big, and obese, respectively), Cmax decreased with the increased age for the same body size until 10 to 12 years old and increased again until 20 years. With the increased body size for the same age groups (3, 5, 10, 12, 15, and 20 years old group, respectively), there was a tendency of decreased Cmax as the body size increased (Fig. 9 and 10).

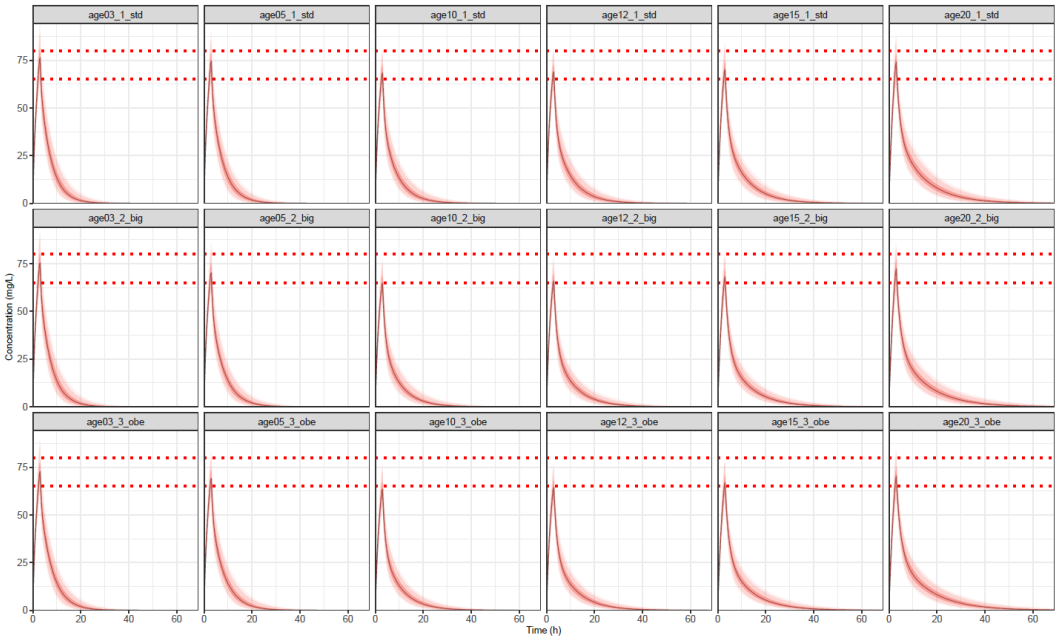
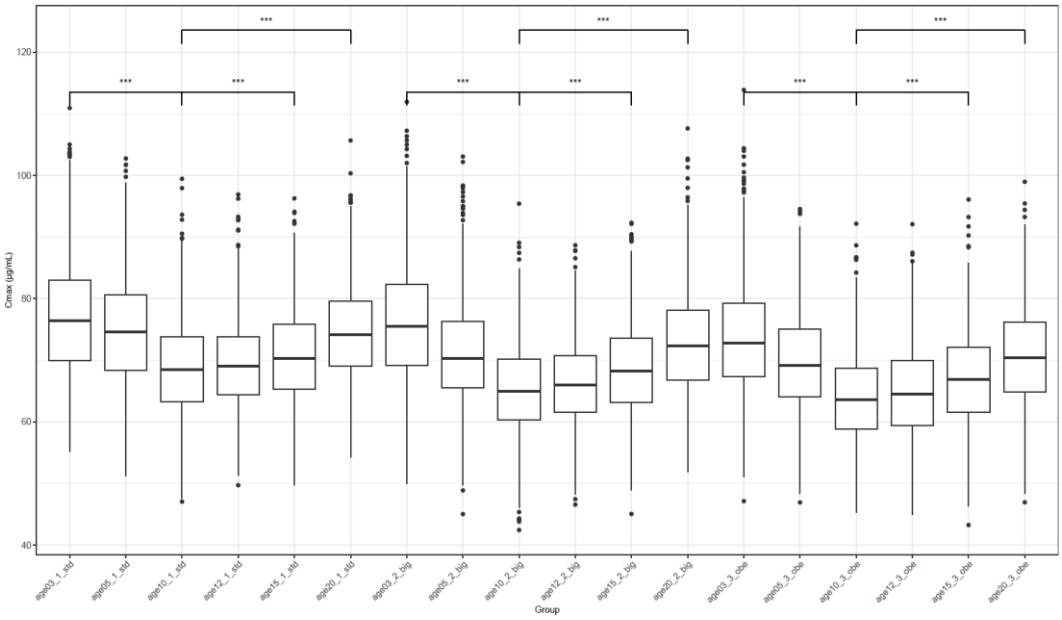


Figure 9. The simulated maximum concentration (Cmax) in the representative patient groups.

All 18 patient groups represent age 3, 5, 10, 12, 15, and 20 years old group and standard, big, and obese body size groups. As the age of the patient groups increases until the age of

10 to 20, the Cmax decreases, however, the Cmax increases again after 12 years old. As the patient groups' body size increases, Cmax decreases in all age groups.

A.



B.

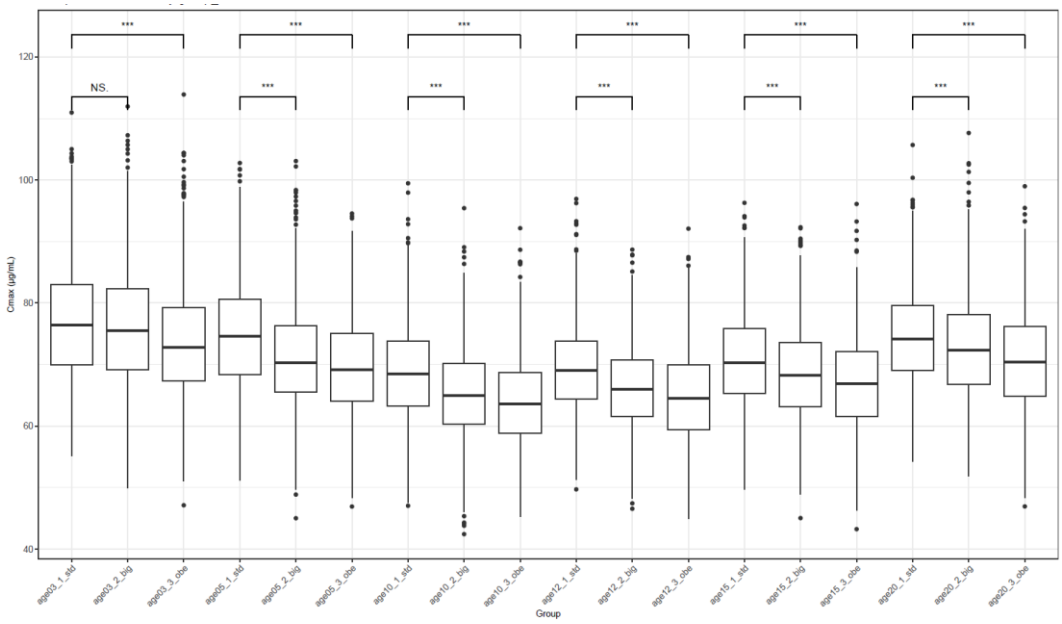


Figure 10. The box plots of simulated maximum concentration (Cmax) in the representative patient groups.

All 18 patient groups represent age 3, 5, 10, 12, 15, and 20 years old group and standard, big, and obese body size groups. A. comparison by age groups. B. comparison by body size. As the age of the patient groups increases from 3 to 10, the Cmax decreases, however, the Cmax increases again until 20 years old. As the patient groups' body size increases, Cmax decreases in all age groups.

The mean AUC decreased from 3 years old to 10 years old and increased thereafter until 20 years old group. With the increased body size for the same age group, there was a tendency of decreased AUC while the body size increased from standard, big to obese group in children but not in adolescents and young adult group (Fig 11 and 12).

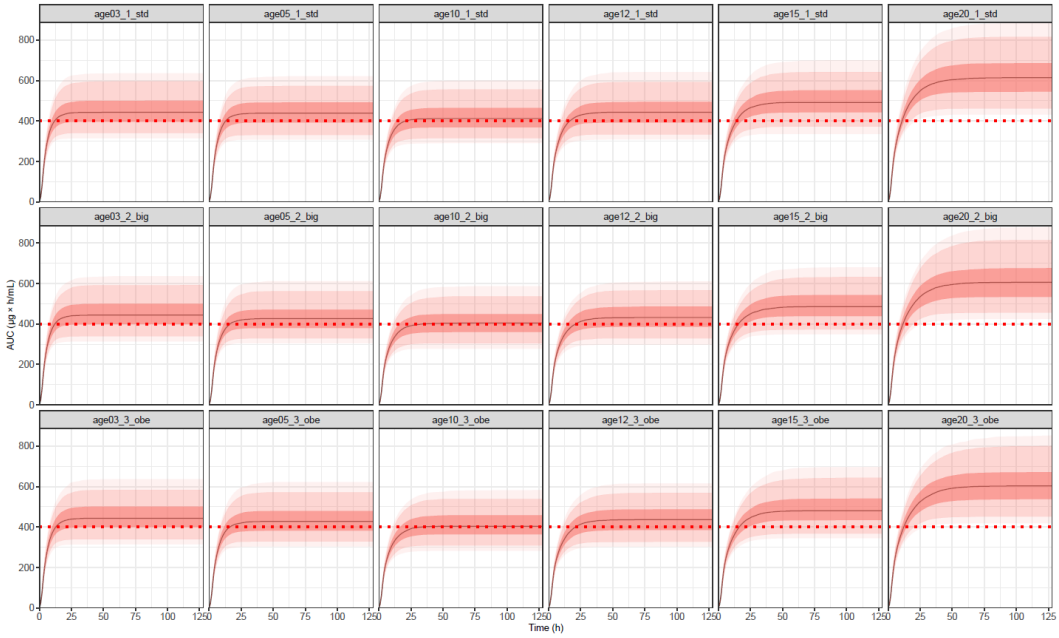
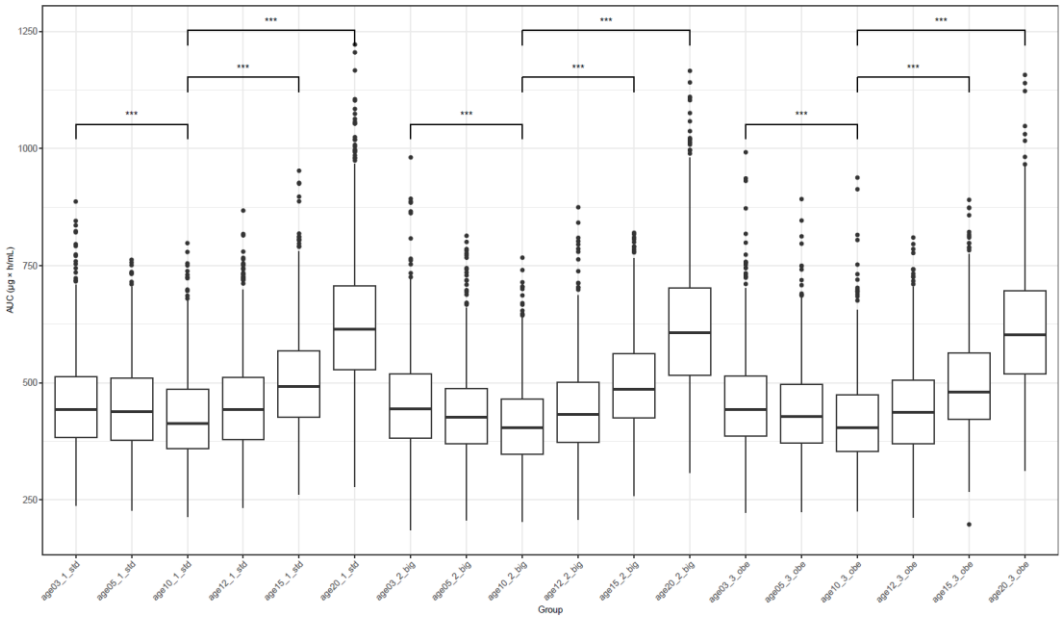


Figure 11. The simulated area under the curve (AUC) in the representative patient groups. All 18 patient groups represent age 3, 5, 10, 12, 15, and 20 years old group and standard, big, and obese body size groups. As the age of the patient groups increases until the age of 10, the AUC decreases, however, the AUC increases after 10 years old. As the patient groups' body size increases, AUC decreases in all age groups.

A.



B.

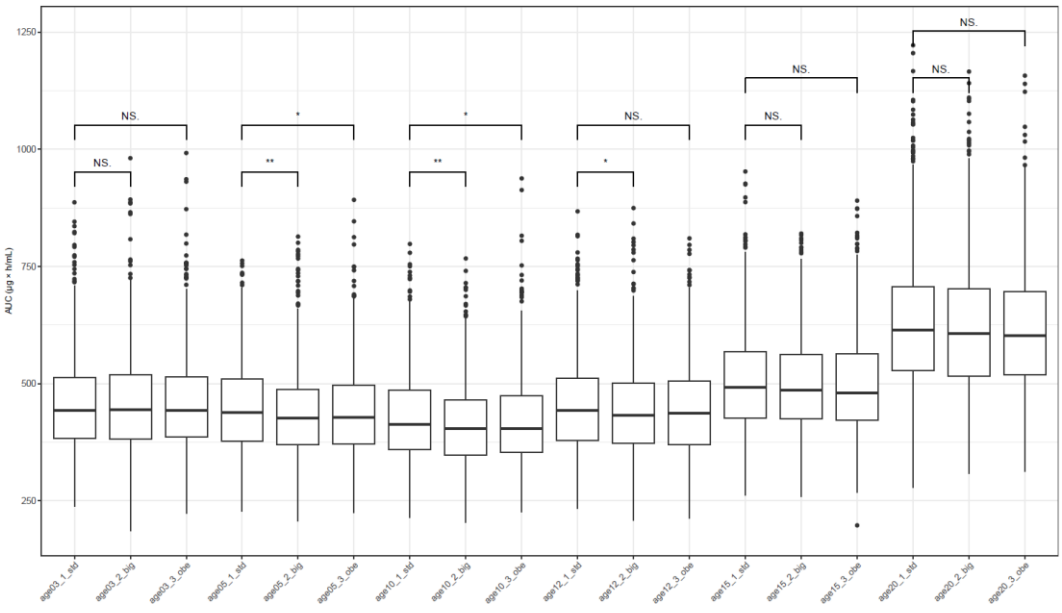


Figure 12. The boxplots for the simulated area under the curve (AUC) in the representative

patient groups.

All 18 patient groups represent age 3, 5, 10, 12, 15, and 20 years old group and standard, big, and obese body size groups. A. comparison by age groups. B. comparison by body size. As the age of the patient groups increased from 10 years old, AUC increased throughout the age in each body size group. As the patient groups' body size increased, AUC decreased in the 5, 10, and 12 years old groups, whereas there was a decreased tendency in the 15, 20 years old age groups but not significant. (NS, not significant; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$)

8. Weight-based dosing regimen

In weight-based dosing regimen. Cmax increased as the age increased for the same body size and the range of increased levels was more evident compared to the BSA dosing regimen (Fig 13 and 14).

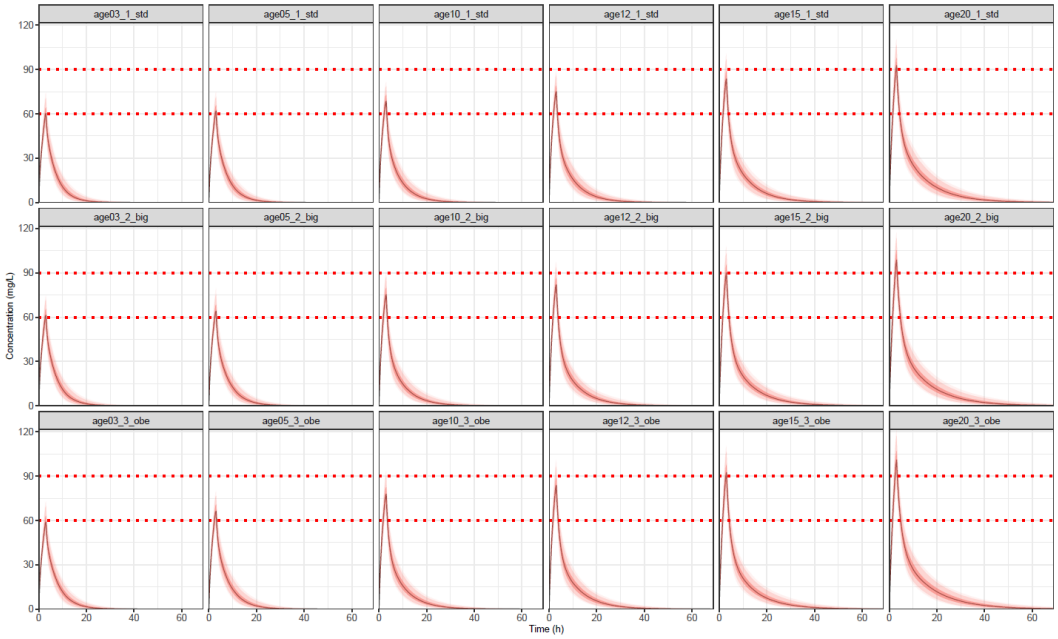
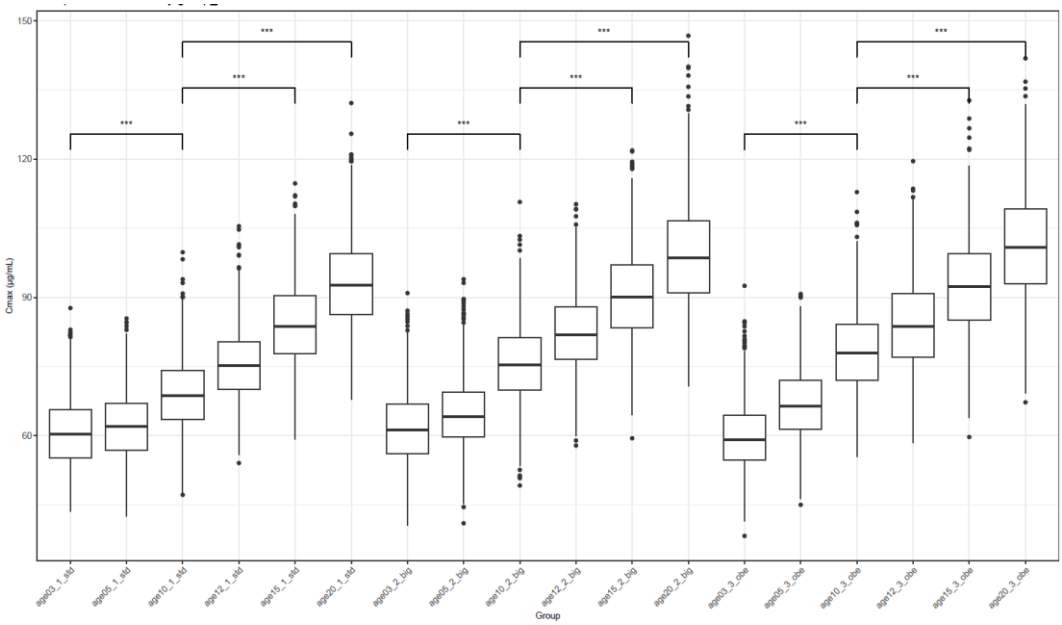


Figure 13. The simulated maximum concentration (Cmax) in the representative patient

groups in weight-based dosing.

All 18 patient groups represent age 3, 5, 10, 12, 15, and 20 years old group and standard, big, and obese body size groups. As the age of the patient groups increased until the age of 20, Cmax increased throughout. As the patient groups' body size increases, Cmax increases in all age groups.

A.



B.

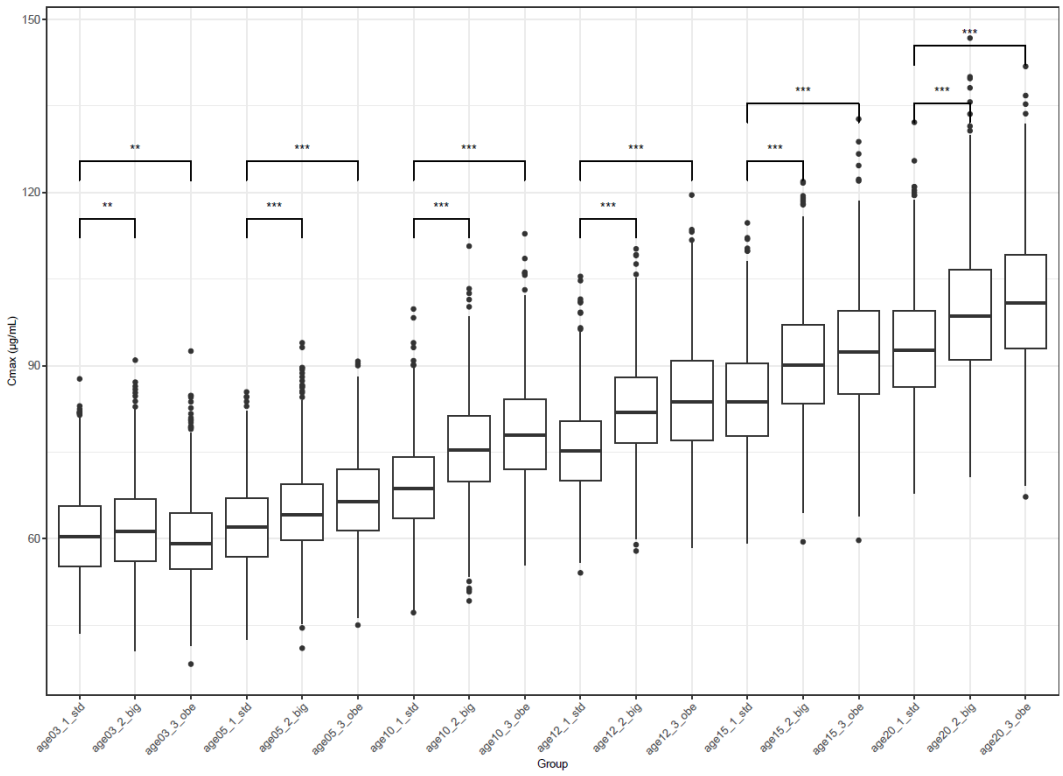


Figure 14. The box plot of simulated maximum concentration (Cmax) in the representative patient groups in weight-based dosing.

All 18 patient groups represent age 3, 5, 10, 12, 15, and 20 years old group and standard, big, and obese body size groups. A. comparison by age groups. B. comparison by body size. As the age of the patient groups increases until the age of 20, Cmax increases throughout. As the patient groups' body size increases, Cmax increases in all age groups.

The AUC also remarkably increased as the age increased for the same body size; the differences among the age groups were exaggerated compared to the BSA-based dosing regimen. For the increased body size for the same age group, AUC was relatively similar but showed an increased tendency (Fig 15 and 16).

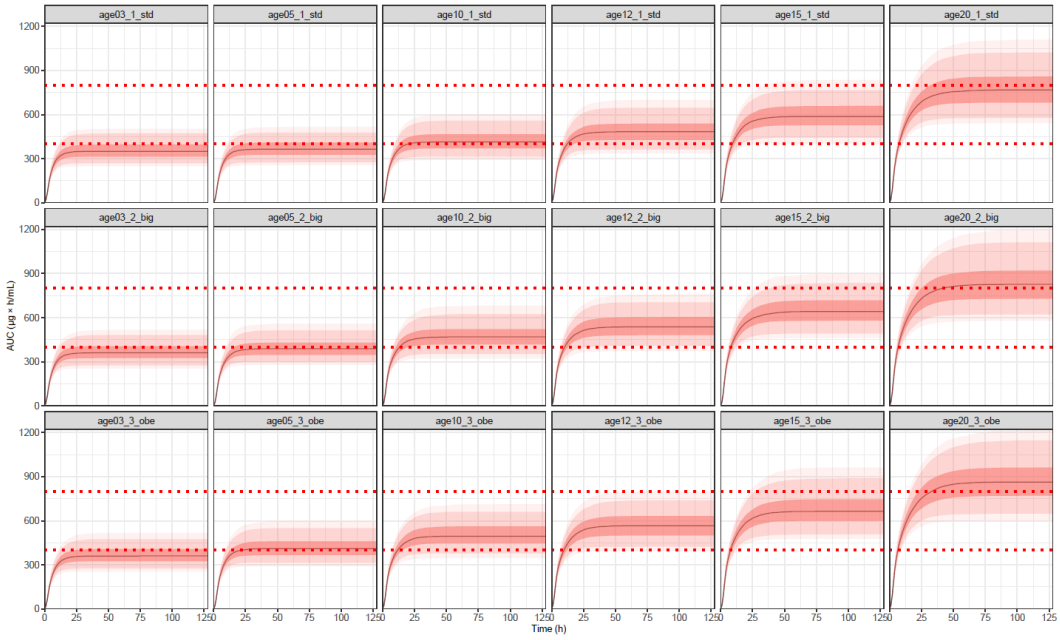
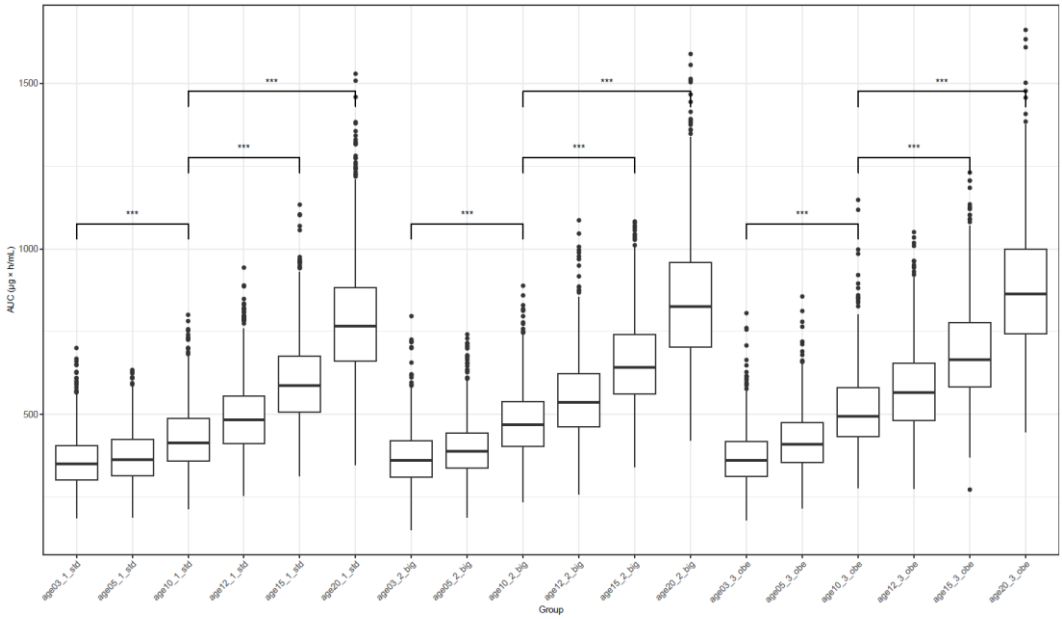


Figure 15. The Simulated area under the curve (AUC) in the representative patient groups in weight-based dosing

All 18 patient groups represent age 3, 5, 10, 12, 15, and 20 years old group and standard, big, and obese body size groups. As the age of the patient groups increased, AUC increased throughout the age in each body size group. As the patient groups' body size increased, AUC increased in 12, 15, 20 years old groups.

A.



B.

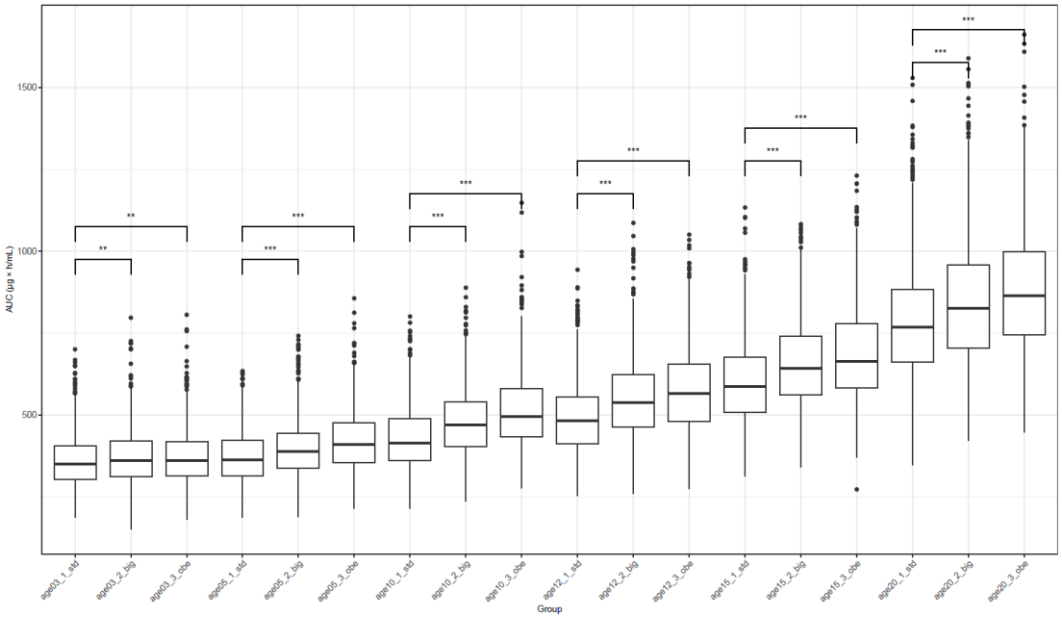


Figure 16. The box plot of the simulated area under the curve (AUC) in the representative

patient groups in weight-based dosing.

All 18 patient groups represent age 3, 5, 10, 12, 15, and 20 years old group and standard, big, and obese body size groups. A. comparison by age groups. B. comparison by body size. As the age of the patient groups increased, AUC increased throughout the age in each body size group. As the patient group's body size increased, AUC increased in all age groups.

9. Simulation for age-appropriate dosing regimen

With the BSA dosing regimen which is most frequently used in clinical practice for oncology, we compared the 3, 10, 15, and 20 years old group with standard body size. With the 100% dose, that is 1200 mg/BSA, Cmax, and AUC were different among the age groups. After optimization, the dose for each age group was to match the Cmax and AUC to the group of 10 years old with other age groups, Cmax and AUC were similar among the age groups. For 20 years old group, the dose was reduced to 70% of the original dose, and the infusion duration was reduced from 180 mins to 80 mins. For 3 years old group, the dose was reduced to 95% (Fig. 17 and 18).

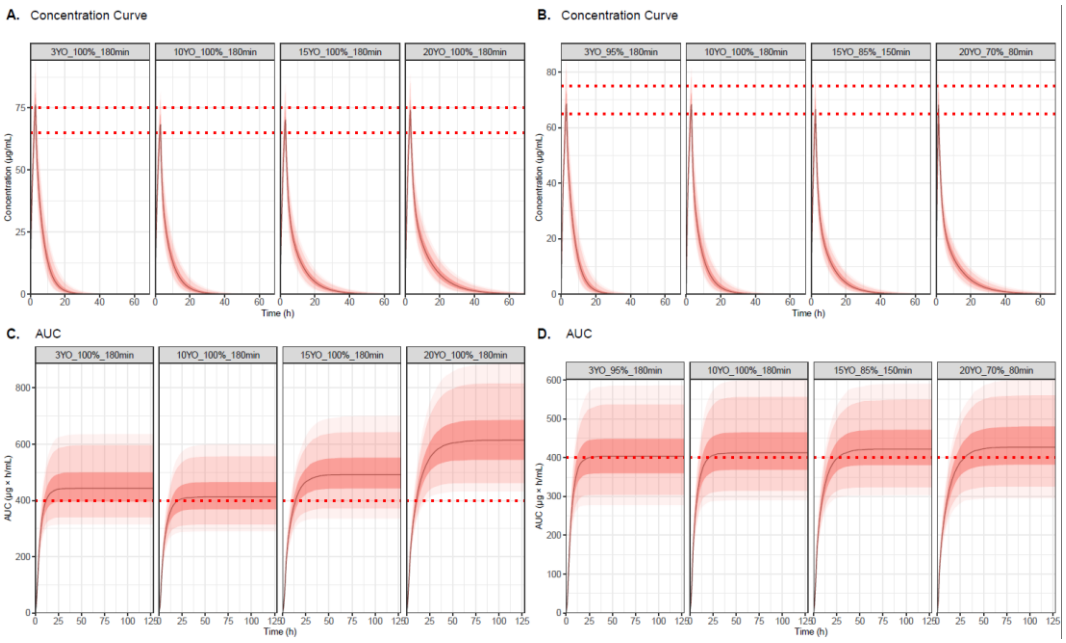


Figure 17. Concentration and area under the curve are simulated by individualized dosing according to the group of patient age.

Each group was administered with body surface area-based dosing. For adjusted dosing, a 5% dose reduction with 180 minutes of infusion was applied to 3 years old group, a 15% dose reduction with 150 minutes of infusion was applied to 15 years old group, and a 30% dose reduction with 80 minutes of infusion was applied to 20 years old group. (A) concentration curve of the unadjusted dosing regimen, (B) the concentration curve of the adjusted dosing regimen, (C) the AUC curve of the unadjusted dosing regimen, and (D) the AUC curve of the adjusted dosing regimen.

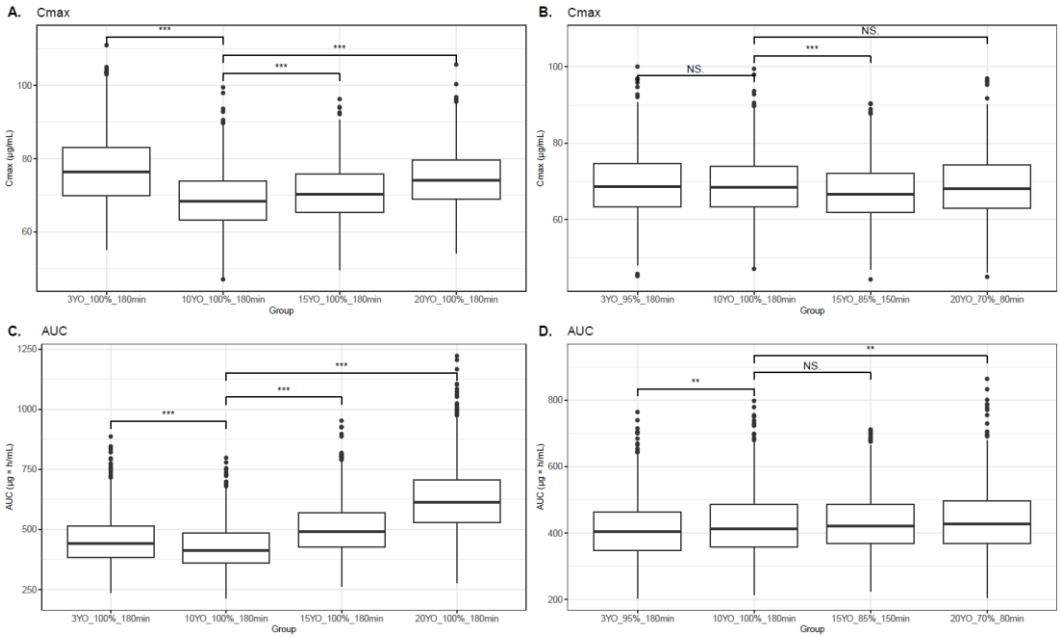


Figure 18. The box plot of concentration and area under the curve simulated by individualized dosing according to the group of patient age.

Each group was administered with body surface area-based dosing. For adjusted dosing, a 5% dose reduction with 180 minutes of infusion was applied to 3 years old group, a 15% dose reduction with 150 minutes of infusion was applied to 15 years old group, and a 30% dose reduction with 80 minutes of infusion was applied to 20 years old group. (A) Cmax of unadjusted dosing regimen, (B) Cmax of adjusted dosing regimen, (C) AUC of unadjusted dosing regimen, and (D) AUC of adjusted dosing regimen.

IV. DISCUSSION

Although cyclophosphamide has been widely used for cancer chemotherapy for more than 50 years, the optimal use of cyclophosphamide for patients of specific age groups and with different and variable body sizes is not fully understood. There are no definite and clear indications for suitable exposure of cyclophosphamide and exact therapeutic windows are known yet[18,21,22]. This partly comes from the complex metabolic pathways and their intermediates or metabolites[18,21]. Therefore, the underlying mechanism of the efficacy and safety of cyclophosphamide are also not understood very well.

Cyclophosphamide is an inactive prodrug and it requires enzymatic activation in the liver as the major organ of activation[21]. It is activated by microsomal mixed-function oxidases. After the activation, phosphoramide mustard is formulated and it acts as a bifunctional alkylating agent. Therefore, cyclophosphamide is a non-phase-specific chemotherapy agent. Only the phosphoramide mustard fraction which is formed intracellularly is considered cytotoxic. The acrolein is formed in the process of the degradation of 4-hydroxy cyclophosphamide through aldophosphamide to phosphoramide mustard and enhances cyclophosphamide-induced cell damage.

In the process of metabolism, cyclophosphamide is directly detoxified by side-chain oxidation, which leads to 2-dechloroethylcyclophosphamide, which accounts for less than 5 percent of total elimination[18,21,23]. The metabolites 4-hydroxy cyclophosphamide and aldophosphamide undergo an irreversible oxidative reaction, resulting in the formation of 4-keto cyclophosphamide and carboxy phosphamide. Although numerous pharmacokinetic studies have been conducted on these intermediates and metabolites of cyclophosphamide, there is a significant limitation in the existing literature. The formation fraction of these cyclophosphamide metabolites has not been adequately defined. As a consequence, in most studies, the pharmacokinetic parameters related to these metabolites are often reported as apparent values. This lack of precise definition affects the accuracy and comparability of the pharmacokinetic data across different studies. Cyclophosphamide and its metabolites are primarily excreted through the urine, with almost complete elimination occurring

within 24 hours after the initiation of treatment. However, it's noteworthy that less than 20% of cyclophosphamide is excreted unchanged. The renal clearance of cyclophosphamide and its metabolites is influenced by urine flow. Despite this urinary excretion, the predominant route of elimination for cyclophosphamide is hepatic. The liver plays a crucial role in metabolizing the drug. Additionally, a phenomenon known as autoinduction is observed with cyclophosphamide treatment. Autoinduction becomes noticeable within the first 24 hours of treatment commencement and leads to a significant reduction in the elimination half-life of the drug, typically resulting in a twofold decrease.

Cyclophosphamide pharmacokinetics are commonly characterized using either a one- or two-compartment model, particularly following a short infusion of the drug. The elimination half-life of cyclophosphamide varies, typically ranging between 5 to 9 hours. Notably, this elimination half-life is shorter in children compared to adults, a variation primarily attributed to increased activity of Cytochrome P450 (CYP) enzymes in children. The heightened CYP activity in the pediatric population leads to a more rapid metabolism of cyclophosphamide, resulting in greater hepatic clearance[18,21]. The systemic clearance ranges from 4 - 5L/h, and non-renal clearance is greater due to renal reabsorption. Vd is 30 to 50L and approximates to the total body water[21]. In this study, we explored a one-, two- and three-compartment model for cyclophosphamide and found that the two-compartment model was the most appropriate. Vd was found to be 6.6 L and 6.7 L for the central and peripheral compartments, respectively, which is approximately 12 L/m^2 based on a typical patient's 1.0 m^2, which is consistent with the previous studies[21]. Clearance was 2.8 L/m^2, which is also consistent with the previous reports, considering that CL was around 10-20% of Vd in previous studies[21].

In general, the most important pharmacokinetic parameters, CL and Vd, are proportional to body size and maturity[24]. It is well known mathematically and empirically that clearance and Vd are proportional to body size[24]. In pharmacokinetics, body weight is usually explored by allometry, and an allometry coefficient of 1 for volume and 0.75 for clearance is generally accepted[24]. Various studies have shown that these multipliers are generally

correct if for no other reason[24]. Therefore in this study, a fixed multiplier of 1 was applied to central and peripheral volume. The multipliers for clearance and peripheral volume were 0.69 and 0.64, respectively, which are consistent with the well-known multipliers for allometry and are considered to be a better fit for the model.

The effects of age as covariates on the pharmacokinetics of cyclophosphamides are known [18,21]. Clearance decreases with age in children, and therefore, the half-life is shorter in children, and longer in adults[18,21]. However, almost all studies are studies on only the children group or adult group, and direct comparison among the age groups is not readily possible[18,21]. There is still insufficient information about the pharmacokinetic profiles through the direct comparison among the age groups such as infants, children, young adults, older adults, and elderly patients[11,14,25]. Generally, maturation completes as the babies approach 2 years old after birth, and the pharmacokinetic profiles agree with the body size thereafter[26]. Body size and profile changes as the human is getting old[25]. The efficacy and toxicity are different in the different age groups, such as infants, children, adolescents, young adults, adults, and elderly patients with the same disease and regimen, which showed a need for dose reduction or intensification[5,27-29]. The body still changes from elderly to a very elderly patient, the personalized chemotherapeutic dosing effort based upon pharmacokinetic profiles in the specific age range continues from the birth to the end of life[30]. Moreover, the information on the AYA is limited because pediatrics is focusing the patient under 10 years old and internal medicine focuses on the patient over 40 to 50 years old[11]. The treatment result and efficacy vary in adolescents and young adults according to the treated regimen that developed in children or older adults[11]. Because of this, more exploration through direct age group comparison on the pharmacokinetic profiles is needed in the specific age groups including extremely young age group, AYA group, or extremely old age group[27,29].

In our study, we enrolled children to young adults to show the covariate effect of age from children to young adults on cyclophosphamide. To predict the efficacy and safety of cyclophosphamide with the various covariates, we evaluated Cmax and AUC. In general,

AUC is the primary pharmacokinetic marker for the prediction of efficacy or safety[31]. The effect of AUC of cyclophosphamide on efficacy has been also studied. AUC is correlated with neutropenia as a pharmacodynamic surrogate or tumor complete response[32,33]. High exposure to cyclophosphamide has been linked to an increased risk of veno-occlusive disease (VOD), a notable toxicity associated with the drug[34]. However other studies reported the inverse relationship between AUC of cyclophosphamide and efficacy or safety[35,36]. Other studies did not show any relationship between AUC and efficacy or safety[37,38]. These conflicting results are partly from the complex cyclophosphamide metabolism and active metabolites[21,32]. As of the age of 10, the clearance of patients over the age of 10 gradually decreased, and accordingly, an increase in AUC was observed. On the other hand, it was confirmed through simulation that Cmax decreased as the age gradually increased from children to adults. Cmax and AUC are major parameters related to pharmacodynamics, and the difference between Cmax and AUC according to age can be explained by the difference in efficiency or toxicity according to chemotherapy[39]. In adolescents and young adults, age is one of the important covariates in pharmacokinetics, and clearance changes around 5 to 12 years old in certain chemotherapeutic agents; vincristine, imatinib, methotrexate, busulfan et cetra[11,31]. This is thought to be influenced by lots of factors such as maturation changes in anthropometric measures, organogenesis, drug disposition, absorption, distribution, elimination, and metabolism[11].

Obesity plays a key effect on the organs in terms of absorption, distribution, metabolism, excretion[40]. This is partly due to altered hepatic metabolic activity such as CYP450, changes in renal functions representative of glomerular filtration rate, or tubular secretion, or absorption process such as accelerated gastric emptying, and distribution profiles composed of increased fat mass or alteration of plasma proteins that bind the drugs[40]. In terms of physiologic change of obesity, the proper dosing for obese patients with cancer should be explored, however, the knowledge is still lacking[40,41]. Dose reduction or capping has been a common practice pattern in oncology for elderly or obese patients[42]. With the low level of evidence, dosing for cancer therapeutic agents should be based upon full

weight-based dosing per body surface area, and not offering dose reduction or capping of the dose, regardless of cancer types or chemotherapy agents[40,41]. No evidence indicates increased toxicity in obese patients when using total body weight for dosing[40,41]. Moreover, these guidelines were published for adult patients, still, there is no sufficient guideline or guidance for pediatric, adolescent, or elderly patients[40,41]. To use an even higher dose of cytotoxic chemotherapy agents than usual in obese patients is more challenging. In this extreme situation such as high-dose chemotherapy with hematopoietic stem cell support, the recently published result shows that through the simulation of Cmax and AUC in standard, large, and obese patients by age group, and AUC decreased as it progressed to obesity in all age groups[43]. It suggests that the effect of anticancer drugs may decrease in obese patients[43]. These results are consistent with the information that it is best to administer the calculated dose based on actual body weight without reducing or capping the dose to the patients regardless of body size even in the high-dose chemotherapy setting, as suggested by recent chemotherapy guidelines in obese patients[40,41]. In our study, AUC decreased in the obese patients whereas Cmax increased. With this finding, reducing or capping doses for obese patients can not be justified.

In addition, the difference between the weight-based dosing regimen and the BSA-based regimen was explored through simulation in this study. When the dose was calculated based on Kg compared to the BSA-based, it was found that the variability of Cmax and AUC was much greater than BSA-based dosing in all age groups. There are well-known three models for scaling of dosing for size; weight-based, surface area-based, and allometry 3/4 power-based dosing[44]. Clearance is underestimated when the weight-based model is used, compared to other models[44]. In the simulation in our study, as the body size gradually increases from children to adults, there is less variation between Cmax and AUC when using the dose calculated by BSA than calculated by kg. Therefore, it is expected to be more appropriate to calculate by BSA in general situations.

The pharmacokinetic profiles themselves may not be directly connected to the efficacy represented by pharmacodynamics[39]. Therefore, it is necessary to study which parameter

of PK is connected to the PD[39]. The most important efficacy indicator is survival rate or response rate, but one of the most well-known PD markers as its surrogate markers is neutropenia or myelosuppression[45]. The myelosuppression model was well established by the study of Freiberg[46]. It is important to analyze whether the pharmacokinetic parameter of cyclophosphamide is connected to PD using this myelosuppression model, but in this study, it is not possible to know a direct association with neutropenia because there were no patients who were given cyclophosphamide alone first. In addition, unfortunately, in this study, the metabolites of cyclophosphamide was not analyzed, since the effective molecules are not cyclophosphamide itself but active metabolites.

This study has several limitations. First of all, the number of enrolled patients was too small, and a suitable model from babies to young adults could not be established. Since the active metabolites of cyclophosphamide were not analyzed, Cmax and AUC of parent agents - cyclophosphamide would not explain the PD properly. The covariate effect of age should be confirmed by external validation under further study. Nevertheless, this study has the advantage of recruiting subjects from ages from children to young adults and building a model, which has led to the relationship between Cmax and AUC according to the increase in body size and age group. As a result of these studies, the strength of this study is that it provides an opportunity to partially understand the effectiveness and increase in toxicity of anticancer cytotoxic chemotherapy, as experienced clinically, even in children, adolescents, and young adults.

V. CONCLUSION

In conclusion, the pharmacokinetic parameters of cyclophosphamide were related to age, weight, and body surface area, which could be applied to present a cyclophosphamide-containing regimen suitable for the patient's age and body size.

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ABSTRACT (IN KOREAN)

집단약동학 모델링을 이용한 소아청소년에서의 사이클로포스파마이드 약동학 특징과 연령에 적합한 약물 투여 전략

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연구목적

세포독성 화학요법은 여전히 암 치료의 중요한 요소이지만 연령과 전신 수행 상태에 따라 요법과 용량은 현재까지 경험적으로 조정되어 왔다. 또한, 청소년 및 청년을 위한 요법은 그동안 과학적인 근거가 부족하여 적절히 개발되어 오지 못하였다. 본 연구에서는 대표적인 세포독성 화학요법제 중 하나인 사이클로포스파마이드의 집단 약동학 연구를 통해 연령별로 적합한 투약 요법을 제안하는 것을 목표로 한다.

방법

실제 암치료 과정 중 수행되는 항암화학요법 중 사이클로포스파마이드를 투여하는 총 38명의 소아, 청소년, 성인이 연구에 등록되었다. 혈액 채혈은 사전 정의된 시점에 따라 전향적으로 수집되었다. 집단 약동학 모델링과 시뮬레이션은 Monolix suite 2021R2를 사용하였다.

결과

이구획모델 및 1차 제거 모형으로 사이클로포스파마이드의 약물 농도가 잘 설명되었다. 체중 28.3kg, 중위수 10세, 체표면적 1.0 m^2인 표준 환자에 대하여, 추정된 중앙 및 주변 구획 분포 용적, 청소율 및 구획 간 청소율은 각각 6553.6 mL, 6661.3 mL, 2828.9 mL/h, 및 4932.1 mL/h 로 추정되었다. 시뮬레이션에서 체표면적 기반 투여 요법은, 3세로부터 10세까지 연령이 증가함에 따라 혈중최고농도(Cmax)와 혈장농도곡선하 면적(AUC)이 감소 하다가, 이후 20세까지 증가하는 것으로 나타났다. 체표면적 기반 요법을 사용한 경우 Cmax와 AUC를 1200 mg/m2의 용량, 3시간 정주요법을 10세 그룹에서 투여하는 경우와 인치시키기 위해서는, 3세 그룹에서 95% 3시간 정주, 20세 그룹에서 70% 80분 정주 요법으로 각각 용량과 주입 시간을 조절 하여야 한다.

결론

사이클포스파마이드의 인구 약동학적 모델을 소아 및 청소년, 청년 그룹에서 구축하였으며 특정 연령대에 적합한 요법을 모델을 이용하여 제안하였다. 모델의 추가적인 고도화 및 향후 검증을 통해 다양한 연령대에 걸친 암 환자에 대해, 모델에 기반한 적절한 연령 적합 용량 제안이 가능할 것이다.

핵심되는말 : 집단약동학, 소아청소년, 청년, 사이클로포스파마이드