POPULATION PHARMACOKINETICS OF HIGH-DOSE CARBOPLATIN

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Introduction

Carboplatin is widely used in the treatment of several malignancies. Whereas for conventional dosing several strategies have been reported to individualise carboplatin dose based on renal function measurements (e.g. creatinine clearance)[1,2], there are only few approaches for high-dose regimens[3,4].

Using a dataset with patients from five different studies, including 13 paediatric patients (age <11 years), we performed a population pharmacokinetic analysis to investigate the influence of patient-specific factors on the pharmacokinetics of high-dose carboplatin.

Patients and Methods

For the population pharmakokinetic analysis data from five different clinical studies were pooled. In all studies patients received a high-dose chemotherapy with autologous stem cell rescue. A detailed description of the study populations and dose regimens is given below.

Table 1: Characteristics of the studies and the study population

Study		1	2	3	4	5	all
Tumour entity		Germ cell cancer	Germ cell cancer	Neuro-blastoma	Ovarian cancer	Various[a]	
Number of patients	*(male/female)*	29 29/0	16 16/0	11 7/4	7 0/7	6 6/0	69 58/11
Infusion duration (h)	*(1/24/96)*	29/0/0	16/0/0	11/0/0	0/7/0	0/0/6	56/7/6
Daily dose (mg)	*median* *(min-max)*	950 (650-1100)	995 (800-1250)	330 (250-435)	2139.9 (1900-2480)	1926 (464-3620)	950 (250-3620)
Total dose per cycle (mg/m²)	*median* *(min-max)*	1500 (1091-1583)	1500 (800-1500)	1473.3 (772-1619)	1300 (1161-1476)	1211.8 (800-2000)	1499.9 (771-2000)
Observations per patient	*median* *(min-max)*	20 (13-23)	8.5 (6-10)	8 (5-10)	14 (5-18)	36.5 (10-81)	14 (5-81)
Number of additional cycles observed[b]		0	0	0	5	7	12
Co-medication with amifostine	*(yes/no)*	0/29	8/8	10/1	1/6	0/6	19/50
Age (yrs)	*median* *(min-max)*	32.9 (20.7-54.7)	33.8 (20.6-60)	4.6 (2.2-9.8)	56.9 (24.9-59.1)	16.9 (2.9-25.6)	30.9 (2.2-60)
Weight (kg)	*median* *(min-max)*	74 (54-105)	81 (63-122)	15.4 (12-37.3)	60 (53-68.5)	53 (14.8-85.7)	69.6 (12-122)
Height (cm)	*median* *(min-max)*	178 (160-191)	185 (176-198)	104 (81-151.5)	165 (163-173)	170.5 (90-189)	176 (81-198)
Body surface area (m²)	*median* *(min-max)*	1.9 (1.6-2.3)	2 (1.8-2.5)	0.7 (0.5-1.2)	1.6 (1.6-1.8)	1.6 (0.6-2)	1.9 (0.5-2.5)
Serum creatinine[c] (mg/dL)	*median* *(min-max)*	0.9 (0.8-1.3)	1.1 (0.8-1.4)	0.4 (0.2-1)	0.7 (0.5-1)	0.6 (0.3-1.1)	0.9 (0.2-1.4)
Creatinine clearance[d] (mL/min)	*median* *(min-max)*	114.5 (72.6-188)	100.2 (70.5-167.3)	59.6 (47.3-109.1)	87.5 (53.8-132)	145 (33.2-194.5)	103.1 (33.2-194.5)

a Osteosarcoma (n=3), plexus carcinoma (n=1), astrocytoma (n=1), rhabdomyosarcoma (n=1).
b Cycle duration = 4 weeks.
c Determined by the Jaffé-Method.
d Calculated according to the Cockcroft-Gault equation for age >12 years and Schwartz equation for age <12 years.

Drug analysis: Platinum was measured in ultrafiltered plasma samples by a validated flameless atomic absorption spectrometry method. Coefficients of variation for both within-day and between-day precision were below 9%. The lower limit of quantification was 20 ng/mL.

PK modeling:

- NONMEM VI 1.2, estimation method: FOCE with interaction.
- The effect of sex, age, body height (HGT), body weight (BW), body surface area (BSA), creatinine clearance (CLCR), serum creatinine, infusion duration (DUR), and co-medication with amifostine were investigated on clearance (CL), central volume of distribution (V1) and intercompartment clearance (Q).
- General additive modeling (GAM) and tree-based modeling (TBM) were applied on 200 bootstrap replicates of the base model. Covariates identified by GAM and TBM in more than 100 replicates were tested within NONMEM by the backward deletion strategy (p<0.005).

Results

- A two-compartment model with zero-order input kinetics (ADVAN3) best described the data.
- A high correlation between ωCL and ωV1 in the final model led to an ill-conditioned ω-matrix (condition no. >2.5x10⁸). This was accounted for by fixing the correlation coefficient to 1 and estimating the ratio of ωV1 and ωCL as a parameter (sdRatio).
- The following covariate-parameter relations were identified:

$$CL(L/h) = 6.57 \cdot (CLCR/103.1)^{0.59} \cdot (HGT/176)^{1.41} \cdot (1+DUR)$$

DUR=0 for a 1h infusion; 0.24 for a 24h infusion; 0.32 for a 96 h infusion

$$V1(L) = 20.4 \cdot (BW/69.6)^{0.81}$$

$$Q(L/h) = 0.83 \cdot (AGE/30.9)^{-0.32} \cdot (HGT/176)^{2.34}$$

- The inclusion of the covariates considerably reduced the unexplained interindividual variability of the respective parameters (see table 2).

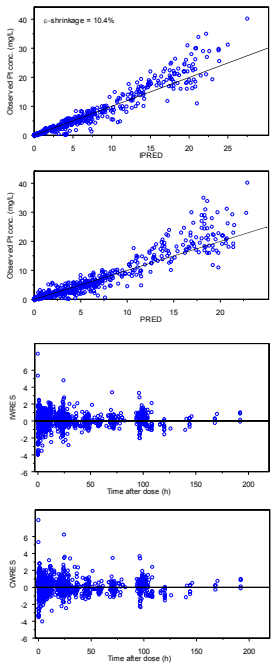

Figure 1: Goodness-of-fit plots

Table 2: PK parameter estimates of the base model, the final model and the bootstrap replicates of the final model

Parameter	Base model	Final model	Bootstrap results (1000 resamplings) Median	95% CI
OFV	-1672.6	-1856.6	-1890.0	(-2581.7- -1290.2)
CL (L/h)	6.31	6.57	6.58	(6.23-6.98)
Q (L/h)	0.76	0.83	0.83	(0.77-0.89)
V1 (L)	17.8	20.4	20.4	(19.6-21.4)
V2 (L)	31.5	32.3	32.7	(29.2-36.5)
CLCRonCL	NA	0.59	0.59	(0.39-0.78)
DURonCL (24h)	NA	0.24	0.24	(0.08-0.39)
DURonCL (96h)	NA	0.32	0.32	(0.10-0.55)
HGTonCL	NA	1.41	1.41	(1.09-1.89)
AGEonQ	NA	-0.32	-0.31	(-0.47- -0.15)
HGTonQ	NA	2.34	2.33	(1.73-2.93)
BWonV1	NA	0.81	0.81	(0.73-0.88)
sdRatio	NA	0.56	0.62	(0.07-6.92)
r(V1,CL)	0.95	NA	NA	NA
r(V1,Q)	0.74	NA	NA	NA
r(Q,CL)	0.63	0.31	0.31	(-0.99-0.99)
IIV CL (%)	50.6	7.0	7.1	(0.67-18.3)
IOV CL (%)	14.7	19.9	18.3	(10.5-22.6)
TPV CL (%)	52.7	21.1	20.3	(16.3-24.4)
IIV V1 (%)[a]	48.2	3.9	4.5	(0.35-12.7)
IOV V1 (%)	16.8	13.4	12.7	(3.99-19.3)
TPV V1 (%)	51.0	14.0	14.2	(8.88-20.6)
IIV Q (%)	32.7	16.5	15.8	(7.3-21.8)
aRV (mg/L)	0.027	0.027	0.027	(0.013-0.040)
pRV (%)	24.1	24.0	24.0	(21.6-26.7)

a $IIV_{V1} = \sqrt{IIV_{CL}^2 \cdot sdRatio^2}$

OFV: Objective function value, **r**: Correlation coefficient, **sdRatio**: ωV1/ωCL, **IIV**: Interindividual variability, **IOV**: Interoccasion variability, **pRV**: Proportional residual variability, **aRV**: Additive residual variability, **TPV**: Total parameter variability ($TPV = \sqrt{IIV^2 + IOV^2}$)

Conclusions

- Creatinine clearance was identified as main predictive factor for carboplatin clearance. This is physiologically sound as carboplatin is mainly eliminated via glomerular filtration.
- Carboplatin clearance increased with increasing infusion duration. This was also observed by other investigators [5,6]. A possible explanation could be that lower maximum concentrations during a prolonged infusion favour irreversible protein binding. The exact mechanism, however, remains to be investigated.
- The presented equation for the calculation of CL should be evaluated prospectively. It could then be used to individualise the carboplatin dose required to achieve a certain target AUC in high-dose regimens.

References

[1] Calvert AH, Newell DR, Gumbrell LA et al. J Clin Oncol 1989; 7:1748-1756.
[2] Chatelut E, Dezeuze A, Lavit M et al. Bull Cancer 1995; 82:946-953.
[3] Shen M,Schilder RJ, Obasaju C et al. Cancer Chemother Pharmacol 2002; 50:243-250.
[4] Kloft C, Siegert W, Jaehde U. Br J Cancer 2003; 8:787-794.
[5] Olver IN, Webster LK, Millward MJ et al. Cancer Chemother Pharmacol 1995; 37:79-85.
[6] Smit EF, Willemse PH, Sleijfer DT et al. J Clin Oncol 1991;9:100-10.

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