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Population pharmacokinetic modeling of cisplatin in patients with small cell lung cancer using informative priors

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Background

- **Small cell lung cance**r is the most aggressive type of lung cancer.
- **Cisplatin + etoposide is a first line of treatment.**
- **Cisplatin dosing** is conventionally adjusted with respect to the **body surface area** (BSA)[1,2].

Objectives

- To study the **therapy with cisplatin** and pharmacokinetics in patients with small cell lung cancer.
- To develop a **population pharmacokinetic model** for cisplatin.
- To **compare** various population pharmacokinetic models of cisplatin.
- To estimate the exposure of patients to cisplatin.

Methods

- 17 patients with small cell lung cancer;
- Plasma sampling: between 7 min and 7 h after the dosing;
- Unbound cisplatin measurement:
  - inductively coupled plasma mass spectrometry (ICP-MS)
- Modeling:
  - NONMEM 7.3[3], FOCE-I;
  - Non-informative data set;
  - Three published models: priors ($Prior, NWPRI);
  - Model development: 1- and 2-compartment models

Patients

Characteristic	Value
No. of patients studied	[a] 17
No. of evaluable courses	[a] 58
No. of cisplatin concentrations	[a] 100
Sex	
	[b] Female (6)
	[b] Male (11)
Age (years)	[c] 63 (51 - 78)
Body weight (kg)	[c] 83 (47 - 98)
Height (cm)	[c] 170 (153 - 183)
[d]Body surface area (m^2)	[c] 2.04 (1.45 - 2.16)
Serum creatinine (µmol/L)	[c] 69 (49 - 103)
[e]Glomerular filtration (mL/min)	[c] 83 (60 - 132)
Cisplatin dose (mg)	[c] 140 (110 - 160)
Cisplatin concentration (µg/L)	[c] 202 (44 - 2613)

[a] Count, [b] Category (count), [c] Median (range), [d] Calculated according the Mosteller equation[4], [e] Calculated according the Wright formula[5].

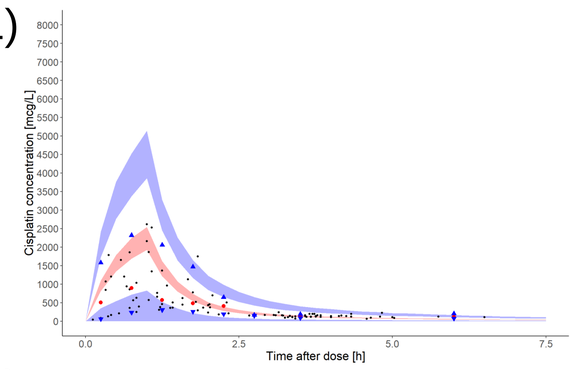
Results

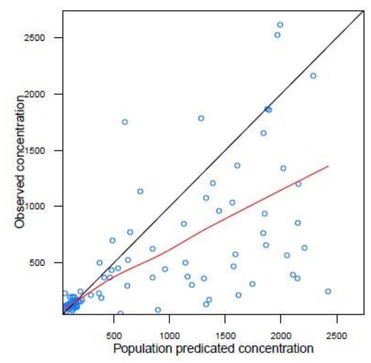
Model comparison

Clinical study	No. of patients	Disease	Dose	Dosing	Assay	Model number	Structural model	Covariates
Urien et al., 2004[6]	43	various types of metastatic cancers	15-80 mg/infusion	30 min IV infusion 5 consecutive days or twice per month	ultrafiltration, flameless atomic absorption spectrophotometry (AAS)	1	2-comp	BSA, ClCr
Chen et al., 2013[7]	41	non-small-cell lung cancer	20 mg/m^2/day	30 min IV infusion 4 consecutive days, cycle repeating in 21 days	ethanol extraction, AAS	2	2-comp	BSA, GROUP
Urien et al., 2005[8]	32	various types of malignant tumors	10-30 mg/m^2	30 min IV infusion or oral administration 5 consecutive days	ultrafiltration, AAS	3	2-comp	BSA
Our study	17	small cell lung cancer	110-160 mg (80 mg/m^2)	60 min IV infusion, cycle repeating in 21 days	ultrafiltration, ICP-MS	4	1-comp	BSA

Visual predictive check | **Goodness of fit** | **Typical CL**

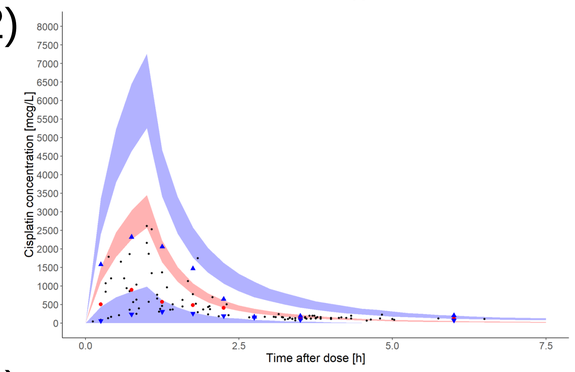
1)

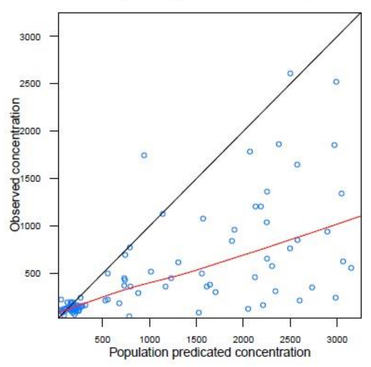




CL = 36.8 L/h

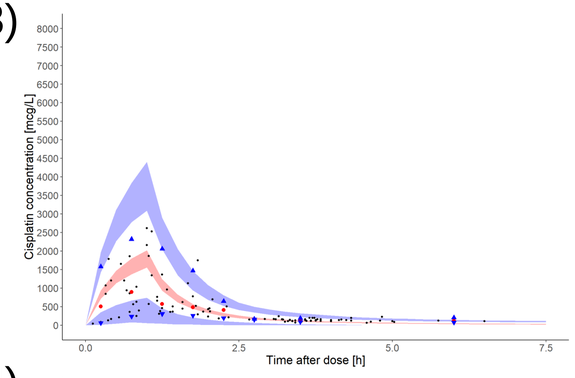
2)

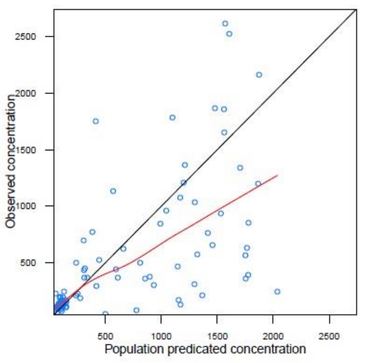




CL = 28.9 L/h

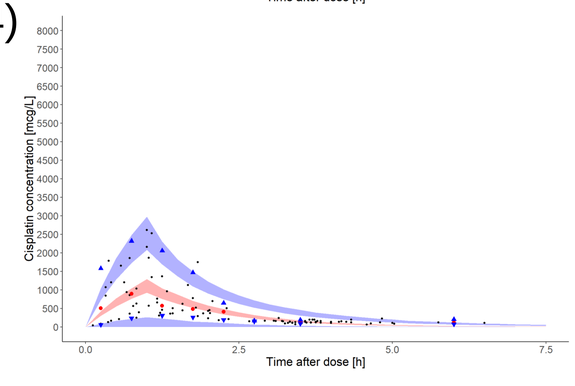
3)

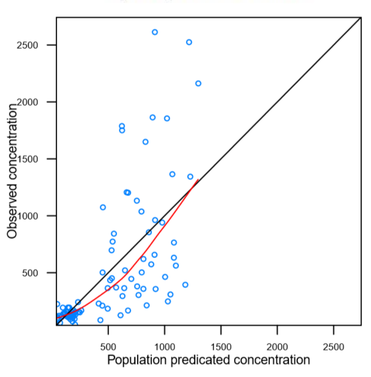




CL = 45.1 L/h

4)





CL = 67.5 L/h

Conclusions

- **1st study** of pharmacokinetics of cisplatin in patients with small cell lung cancer.
- The assessed pharmacokinetic **models of cisplatin did not fit our data well (underestimated the clearance).**
- BSA was a significant covariate.
- High variabilty in estimated exposure between models.

References

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