External Validation of a Model Based on Cystatin C to Predict Carboplatin Clearance

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Objectives:

The individual dosing of drugs that are mainly eliminated unchanged in the urine is made possible by assessing renal function. Carboplatin is one of the drugs for which elimination is most dependent on glomerular filtration rate (GFR). The formulas currently used for individual carboplatin dosing are all based on serum creatinine (SCr) as the unique biological covariate (together with demographical and morphological covariates) [1, 2]. Thomas *et al.* [3] recently proposed a formula including plasma cystatin C level (CysC), an other endogenous marker of GFR.

A clinical trial (Optimum Carbo) was conducted in 12 centers in France to optimize administration schedule as to maximize efficiency while having the more acceptable toxicity. On the 400 patients of this trial, 260 were included in an ancillary study which aim at assessing Thomas formula, via external validation methods.

Method:

Patients were receiving 1 hour-infusion of carboplatin as part of established protocols, for the treatment of various cancers. 52 patients underwent monochemotherapy, and 208 polychemotherapy. In polychemotherapy protocols, carboplatin was associated with taxol (132 patients), VP16 (26 patients), gemcitabine (14 patients), docetaxel (8 patients), vinorelbine (8 patients), 5-FU (6 patients) or other drugs (14 patients). The primary tumor sites were ovary (107 patients), uterus (31 patients), broncho-pulmonary (26 patients), soft tissues (25 patients), upper aerodigestive tract (11 patients), bladder (11 patients), breast (9 patients), unknown (12 patients), and other (28 patients).

Four blood samplings were taken at the first treatment cycle, at time zero (before administration), 5 min before the end of infusion, 1, and 4 hours after the end of infusion. After immediate centrifugation at 1500 *g* for 10 minutes at 4°C, the plasma was separated and ultrafiltered using the Centrifree® YM-30 device (Amicon product, Millipore, Saint-Quentin-en-Yvelines, France), at 4°C for 20 minutes at 2000 *g*.

Carboplatin was dosed by means of flameless atomic absorption spectrophotometric analysis.

A population pharmacokinetic analysis was performed using the nonlinear mixed effect modeling NONMEM program and FOCE estimation method. Data from 260 patients were used to evaluate Thomas formula, which takes into account SCr, CysC, body weight (BW), age, and sex (190 females and 70 males). All other covariates are described nearby.

First, individual POSTHOC CL were compared to those obtained by the Thomas formula, in order to evaluate the predictive efficiency of this formula on an external validation dataset.

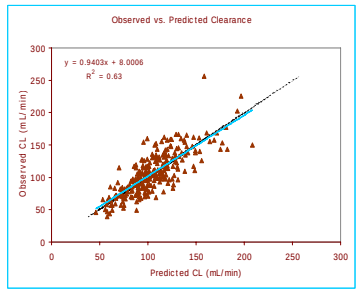
Then, a covariate analysis was performed in order to determine the typical value of those five parameters. The final covariate equation is under, compared to, in brace, those of Thomas *et al.*

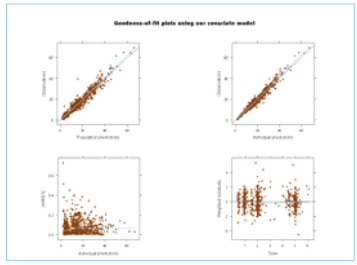
Patients characteristics (190 females and 70 males; BW, body weight; SCr, serum creatinin; CysC, cystatin C)

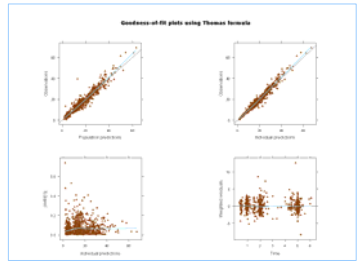
	Amount (mg/L)	BW (kg)	Height (cm)	Age (years)	SCr (µmol/L)	CysC (mg/L)
Min.	194.0	40.00	146	21.00	34.00	0.4660
Median	530.0	62.00	163	60.00	71.50	0.8225
Mean	561.2	64.47	164	59.13	76.85	0.9161
Max.	1600.0	123.00	189	83.00	244.00	2.6200

	Observed CL – Predicted CL*
MPE (%)	1
5th percentiles (%)	-25
95th percentiles (%)	+37
MAPE (%)	14

* According to Thomas formula (MPE, Mean Predictive Error; MAPE, Mean Absolute Predictive Error)



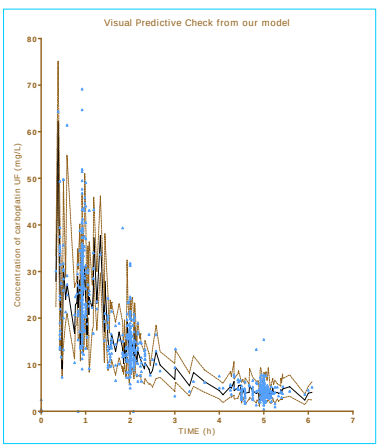


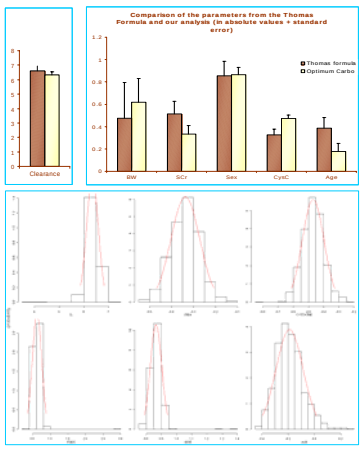


The final covariate equation obtained from the data of Optimum Carbo study was:

$$CL(mL/min) = 105.5\{110\} * (SCr/75)^{-0.332\{-0.512\}} * (CysC/1.00)^{-0.473\{-0.327\}} * (BW/65)^{0.616\{0.474\}} * (age/56)^{-0.178\{-0.387\}} * 0.864\{0.854\}^{sex},$$

with SCr in µmol/L, CysC in mg/L, BW in kg, age in years, and sex = 0 for male, and {*vs. previous value of Thomas formula*}.





Results:

The figure above shows the correlation between observed carboplatin clearance and the value calculated from the final covariate equation (obtained from the Thomas formula) for the 260 patients. The r^2 value between observed clearance and calculated clearance from this equation was 0.63. Bias and precision were respectively +1% and 14%. By comparison, bias and precision corresponding to the final covariate equation were –0.2% and 14%, with $r^2 = 0.65$.

There was no reliable difference between the goodness-of-fit plots from the data analyzed with the Thomas formula and analyzed by our covariate model. The structural pharmacokinetic model, resulting from our data, gives parameters very similar to those of Thomas formula, as shown upper. The only important difference comes from the CI 95% of the parameter related to the age [-0.36;0.004], which slightly overlaps zero. This difference was confirmed by a visual check of bootstrapping results. But when the same analysis is performed without the covariate age, the difference in the objective function values is significant (*p-value* < 5 ‰). To confirm whether this covariate was pertinent or not, a Visual Predictive Check was managed and showed that most of the concentrations simulated were in the confidence interval.

Conclusion:

External validation is the highest degree of validation for PK model. The Thomas formula has been validated at a multi-center level. These results confirm definitively the benefit of cystatin C as a marker of renal elimination of drugs. However, it should be used with other morphological and demographical covariates. Serum creatinine and cystatin C are not thus completely redundant marker of GFR. We propose to use the final covariate equation to individually adapt carboplatin dosage.

References:

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