Prise en compte de la pharmacocinétique dans la prescription des médicaments anticancéreux

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Introduction

Adaptation individuelle des doses

- limite de la surface corporelle
- variabilité pharmacocinétique interindividuelle

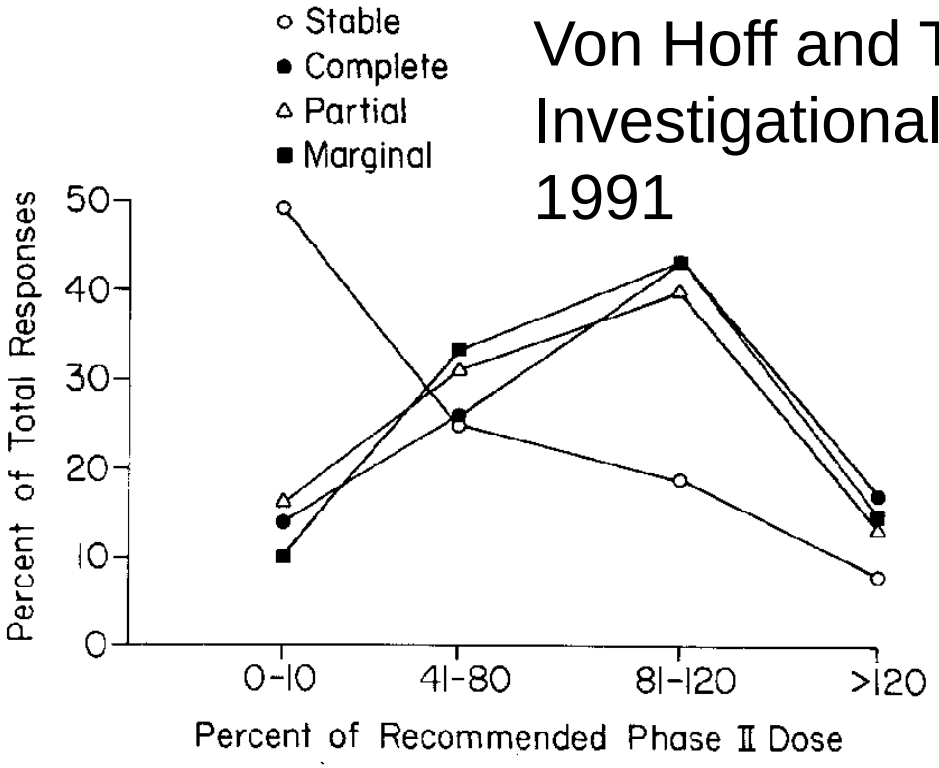
« More is better »

- “more drug” pour plus d’effet thérapeutique
- “more information” pour mieux adapter la dose

Cytotoxiques – thérapeutiques ciblées

Prise en compte des caractéristiques pharmacodynamiques

Response rates in phase I



Von Hoff and Turner, Investigational New Drugs 1991

Fig. 4. Distribution of percent of total responses in phase I study according to percent of recommended phase II doses.

Dose or Concentrations ?

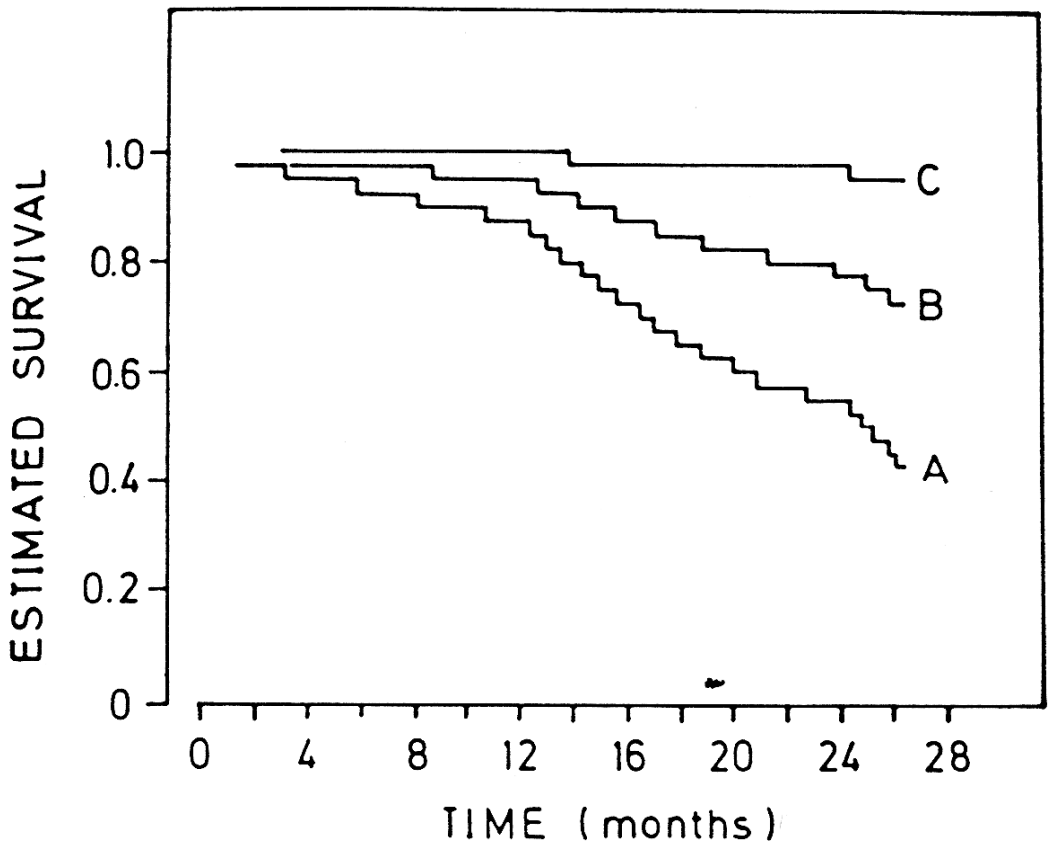
- There are correlated: AUC = Dose/CL

(AUC= area under the curve of plasma versus time concentration = global exposure of a patient to a drug ; CL = clearance of elimination of the drug)

- Is there a benefit to control plasma drug concentrations ? Or Dose is enough ?

- Response: it is largely dependant of the inter-individual variability (IIV) on CL

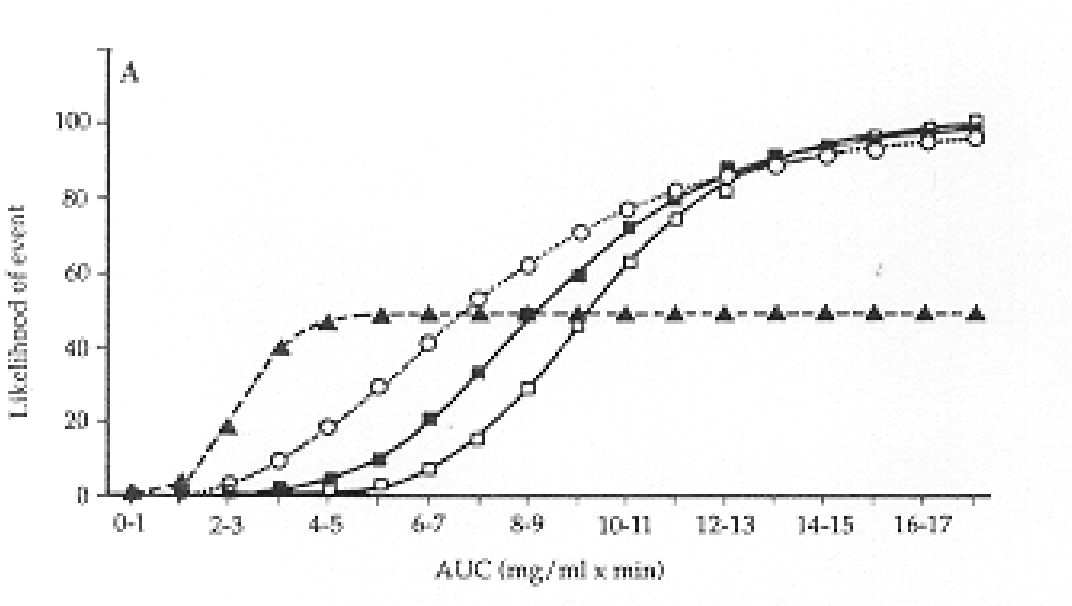
6-MP et LAL: survie et AUC plasmatique



AUC moyenne de 100 (A), 200 (B) et 400 (C) ng de 6-MP/mL/h
[Koren et al, New Engl J Med 1990]

Carboplatine et cancer ovarien

[Jodrell et al, J Clin Oncol 1992]



Toxicity: grade ≥3 thrombocytopenia (■)

Efficacy: Likelihood of response(♦)

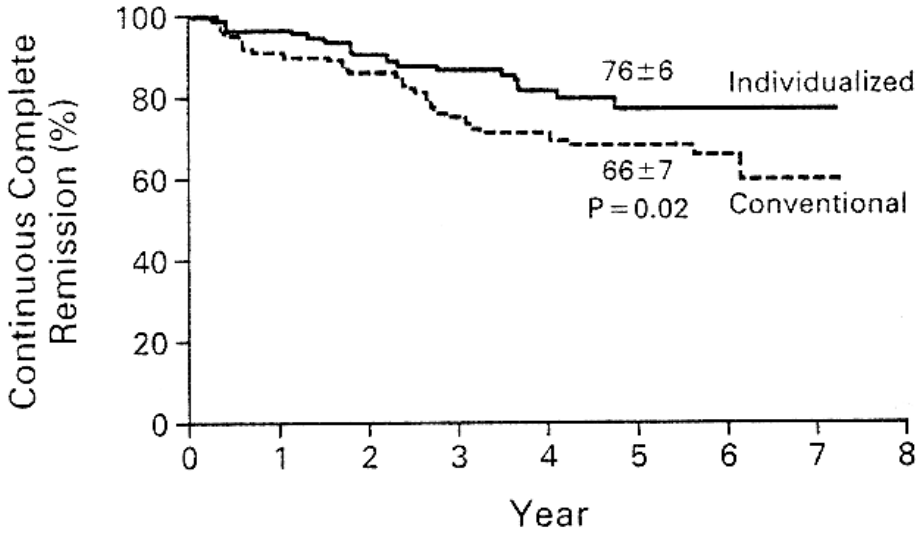
=> Individual dosing of Carboplatin :

Dose (mg) = predicted CL x target AUC

AUC better than Dose:
Proof of concept: Evans et al

New Engl J Med 1998

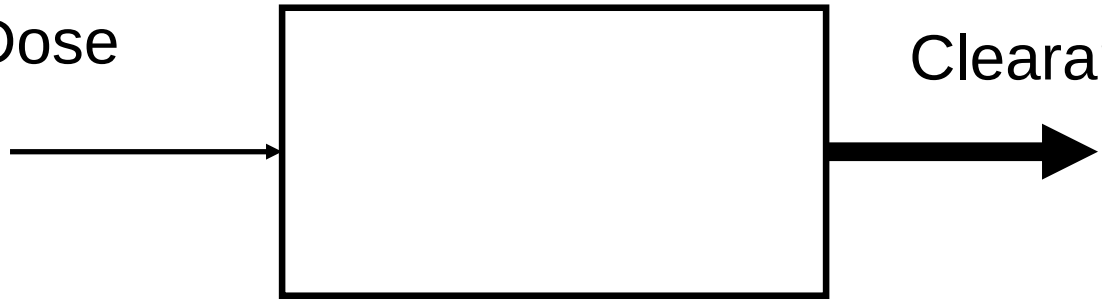
Childhood Acute Lymphoblastic Leukemia
High-dose methotrexate – Teniposide – Cytarabine



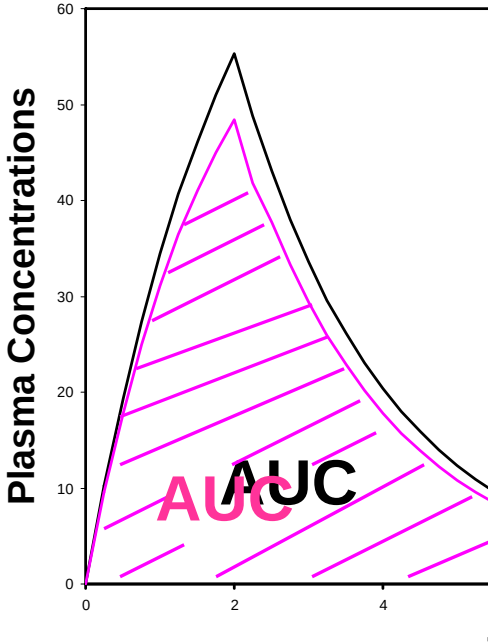
individualized: AUC corresponding to 50th to 90th percentile of conventional dose (per m²)

Low IIV: expected in Phase 1 study

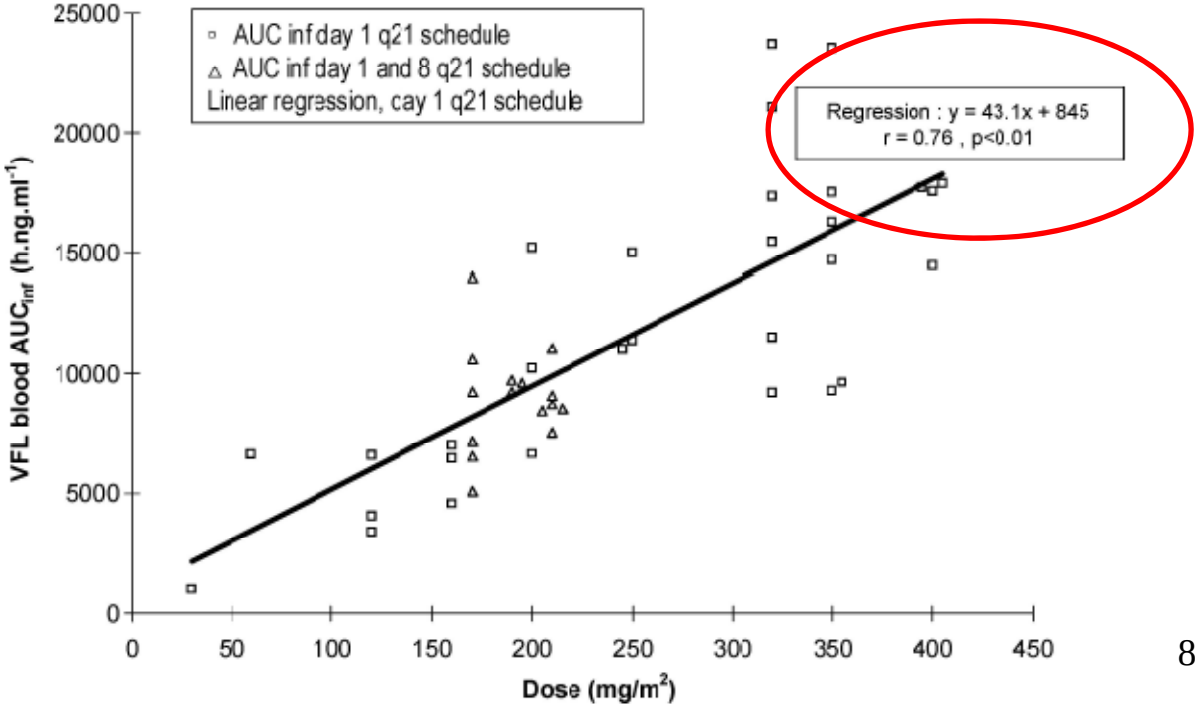
(F) x Dose



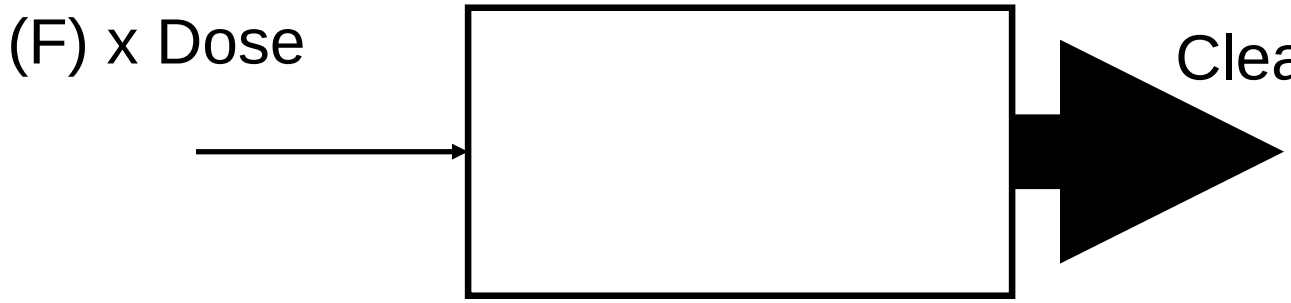
Clearance

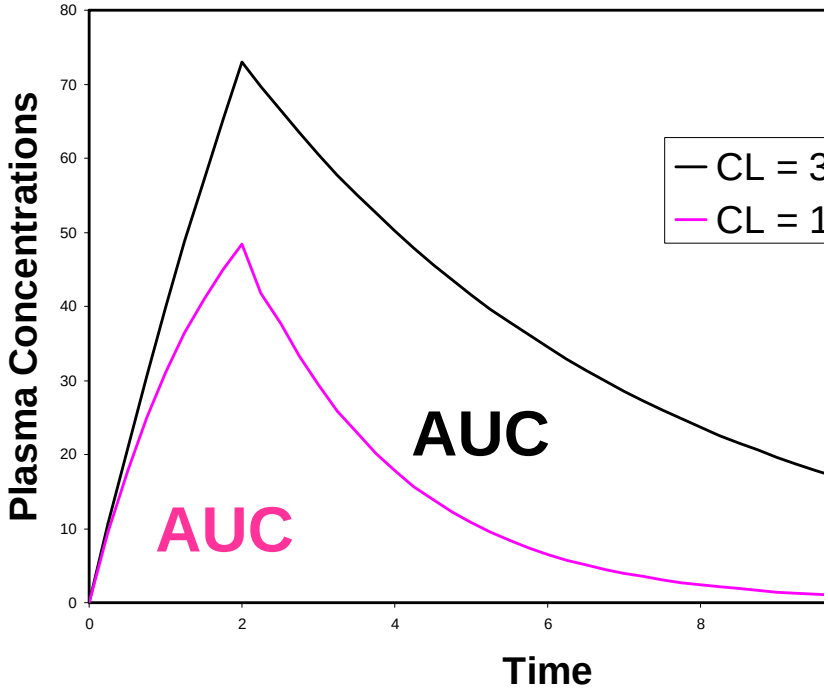


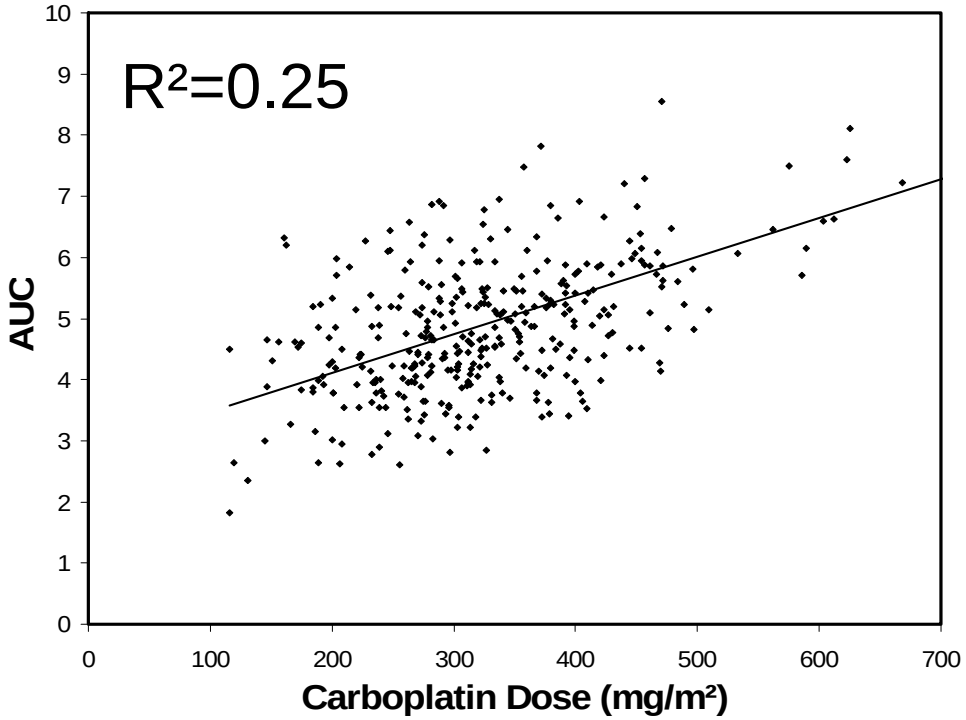
R^2=0.58



Large IIV: observed in clinical practice







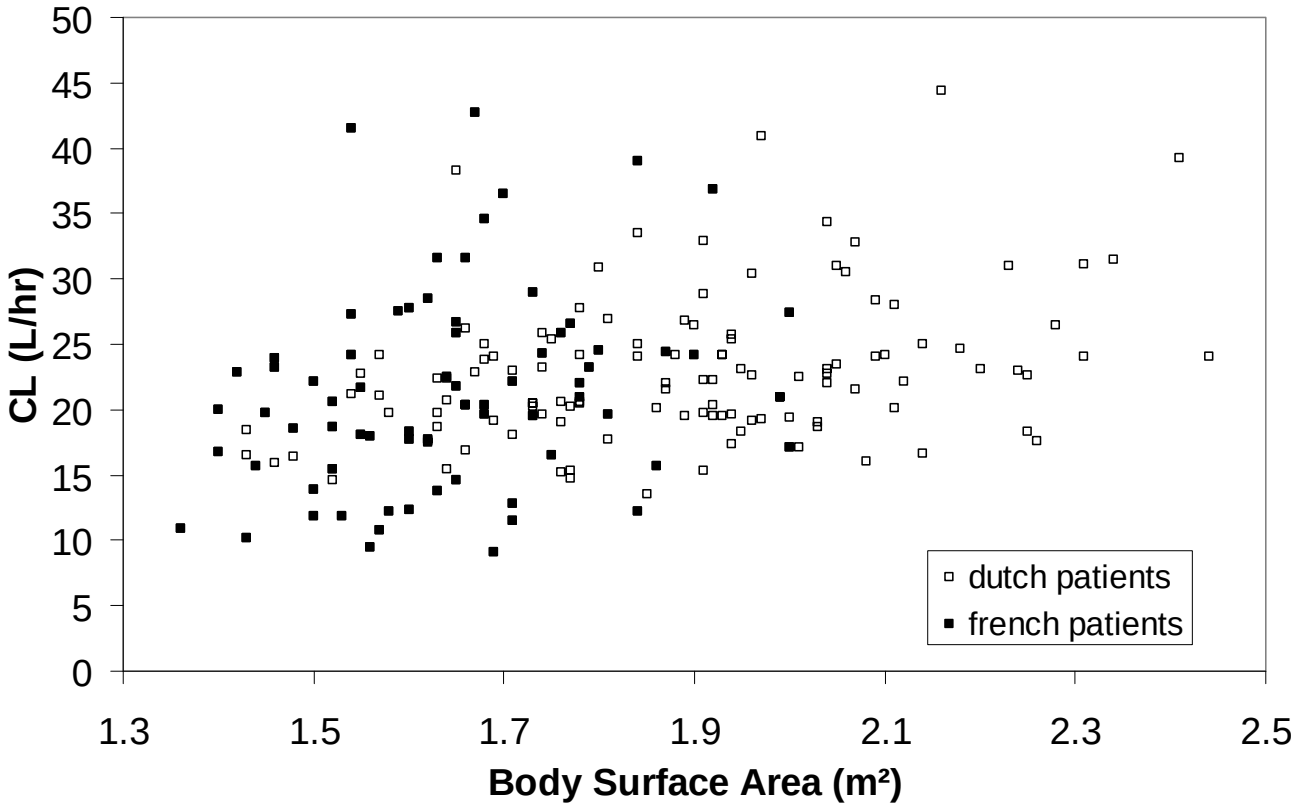
Méthodes d'adapation individuelle des doses

- Surface corporelle
- Prescription en AUC pour le carboplatine
- Exploration phénotypique ou génotypique pour le 5-fluoro-uracile
- Suivi des concentrations plasmatiques et hautes doses ; les « inibs »

Dose en mg/m²

- Avantages
  - Individualisation de la dose
  - Onco-pédiatrie: capacités d'élimination (clairance, CL) corrélées morphologie
  - Reproductible: équation de Dubois
- Inconvénients
  - Patients adultes: CL n'est que rarement corrélée à surface corporelle

Exemple: topotécan



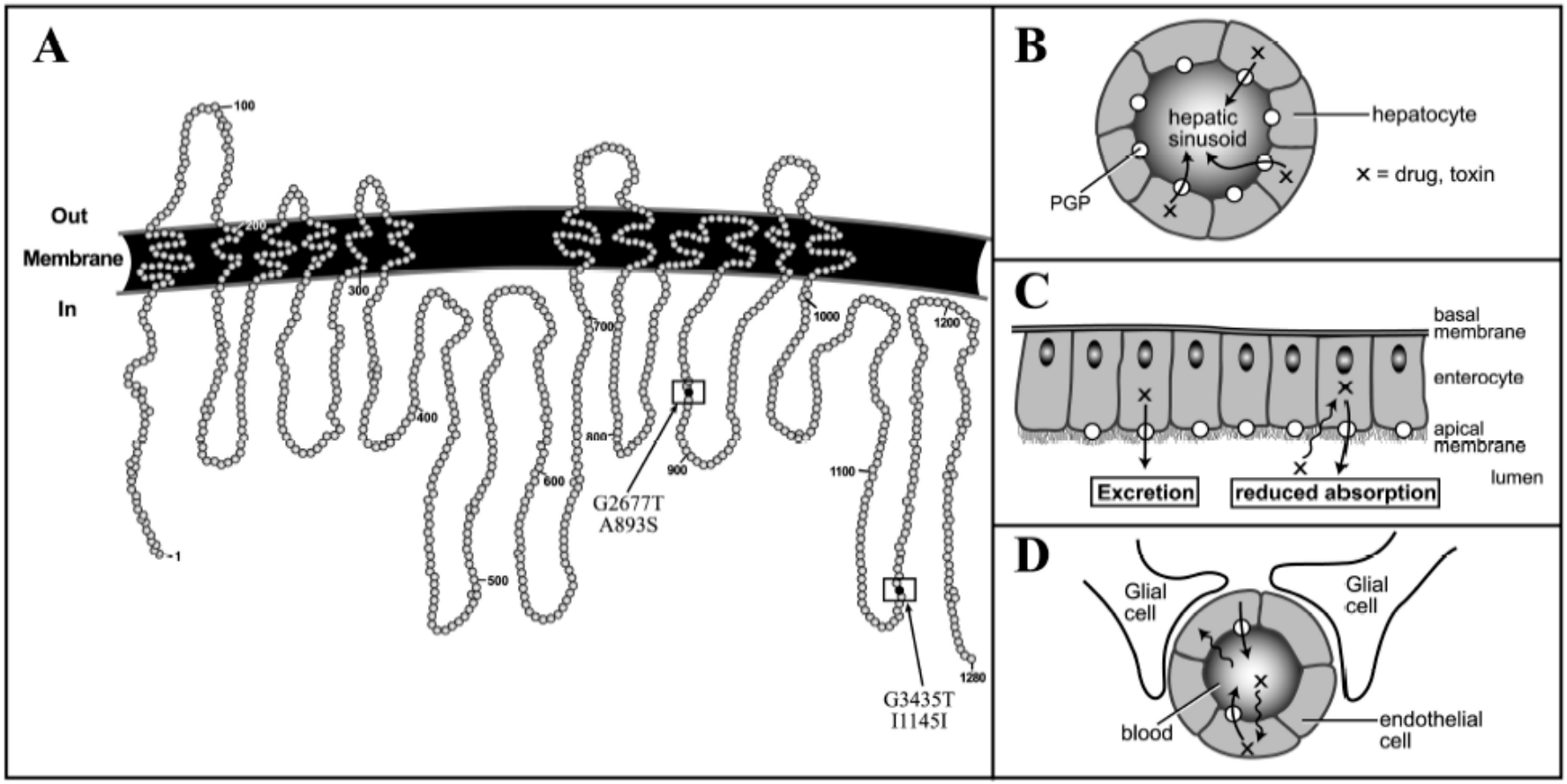
variabilité inter-individuelle

- élimination rénale
  - fonction rénale (filtration glomérulaire)
  - sécrétion tubulaire (transport actif)

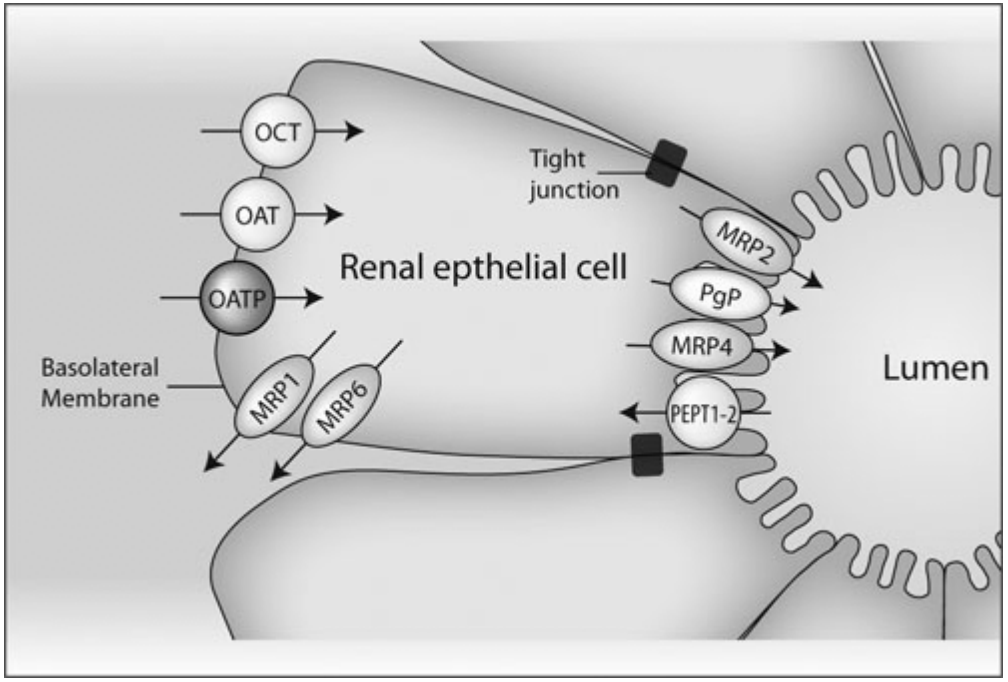
- élimination non rénale
  - métabolisme hépatique
  - transport au niveau biliaire et digestif: ABC transporteurs (glycoprotéine P)

Expression de la P-gp (ABCB1)

[Thomas et al, Curr Top Med Chem 2004]



Sécrétion tubulaire rénale



Élimination rénale: méthodes de prédictions de CL

- Exemple (extrême) du carboplatine
  - Prédiction de CL par équations (Calvert, Cockcroft-Gault, Chatelut)
  - Créatinine sérique, poids, âge, sexe
  - Choix de l'AUC

Carboplatin PK studies
as an example in term of methodology comparison

Calvert equation (CLcarbo = GFR + 25 mL/min) was developed by a 2-stage approach [J Clin Oncol 1989] :

1) successive determinations of carboplatin CL (from AUC determined by trapezoidal rule)

2) linear regression between CL and GFR (Glomerular Filtration Rate determined by ^{51}Cr-EDTA clearance)

We applied the population PK method [J Natl Cancer Inst 1995]:

simultaneous analysis of PK data (conc vs. time) and covariates of 34 patients (using a two-compartment model and proportional inter-individual variability)

$$CLcarbo = 0.134.weight + \frac{218.weight\ (1 - 0.00457.age).(1 - 0.314.sex)}{serum\ creatinine\ level\ (\mu M)}$$

Two main limits

- Serum creatinine is also dependent of its production (muscular mass), and nutrition status ; obese, and underweight patients
- Scr: bias between assay methods (up to 40% of difference)
- Clin Cancer Res 2006:

Flat Dosing of Carboplatin Is Justified in Adult Patients with Normal Renal Function

Corine Ekhart,[1] Milly E. de Jonge,[1] Alwin D.R. Huitema,[1] Jan H.M. Schellens,[2,3] Sjoerd Rodenhuis,[2] and Jos H. Beijnen[1,2,3]

Facteurs d'hétérogénéité des pratiques

exemple: Patient (femme, 82 kg, 1.8 m², 63 years)

Creatinine assay	126 µM (non compensated Jaffé)	91 µM (enzymatic assay)	+38%
Equation to predict CL	Calvert equation	Chatelut equation (no correction for obesity)	+10%
Target AUC	4	5	+25%
	310 mg	**540 mg**	**+74%**

More information: Cystatin C plasma level

- Small Protein (120 amino-acids) expressed in all nucleated cells
- Marker of Glomerular Filtration Rate (GFR)
  - filtered
  - not secreted
  - completely reabsorbed and catabolised within the tubular cells
- Nephrology: conflicting results about cystatin's performance compared to creatinine

Mono-center study ; 45 patients

Cystatin C as a New Covariate to Predict Renal Elimination of Drugs
Application to Carboplatin

Fabienne Thomas, Sophie Séronie-Vivien, Laurence Gladieff, Florence Dalenc, Valérie Durrand, Laurence Malard, Thierry Lafont, Muriel Poublanc, Roland Bugat and Etienne Chatelut

[Clin Pharmacokinet 2005]

Carboplatin CL (mL/min) =

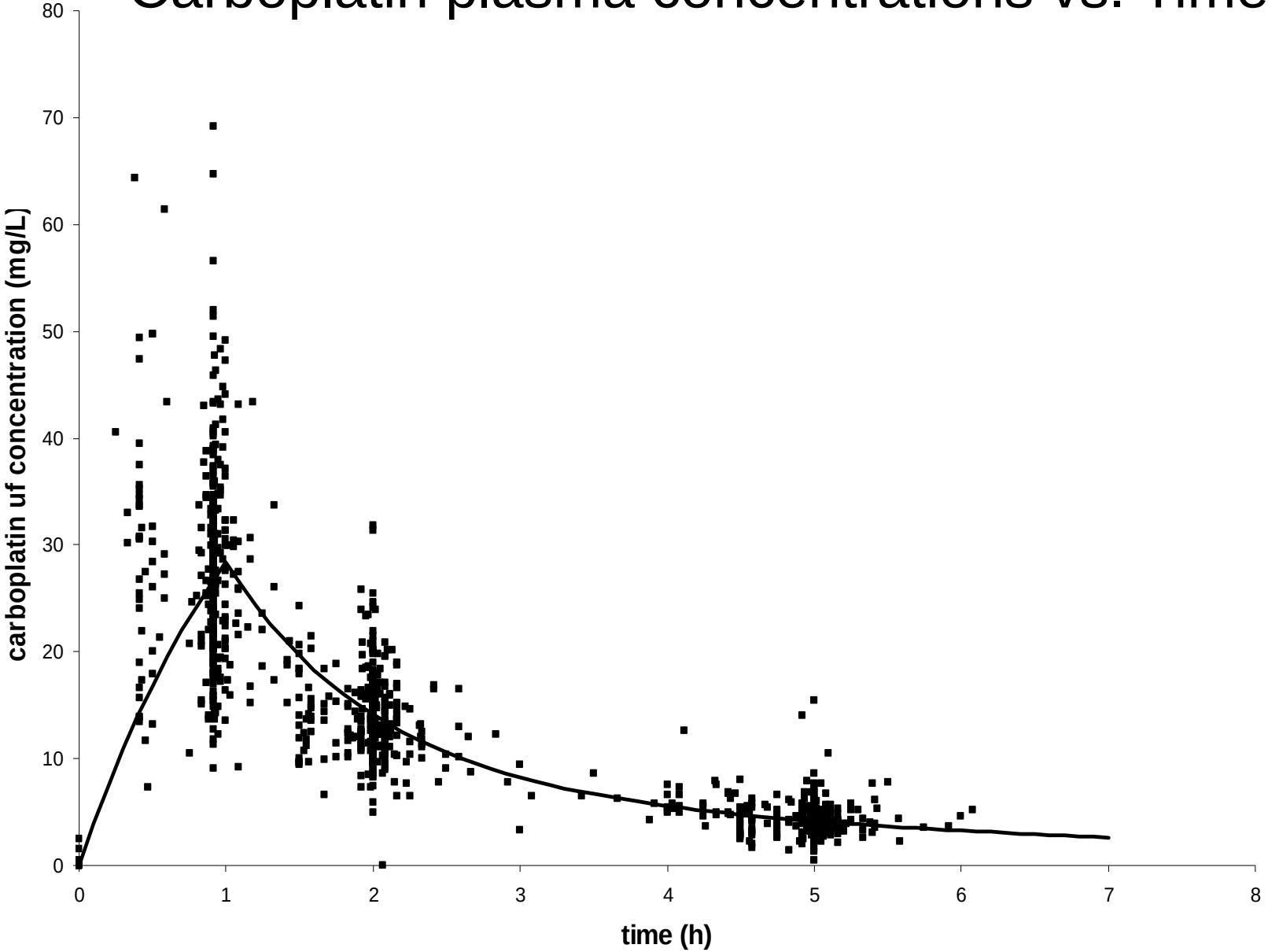
$$110.\ (SCr/75)^{-0.512}.(cysC/1)^{-0.327}.(BW/65)^{0.474}.(AGE/56)^{-0.387}.\ 0.850^{SEX}$$

with SEX = 0 if male, =1 if female, SCr in µmol/L, cysC in mg/L, BW in kg and AGE in years

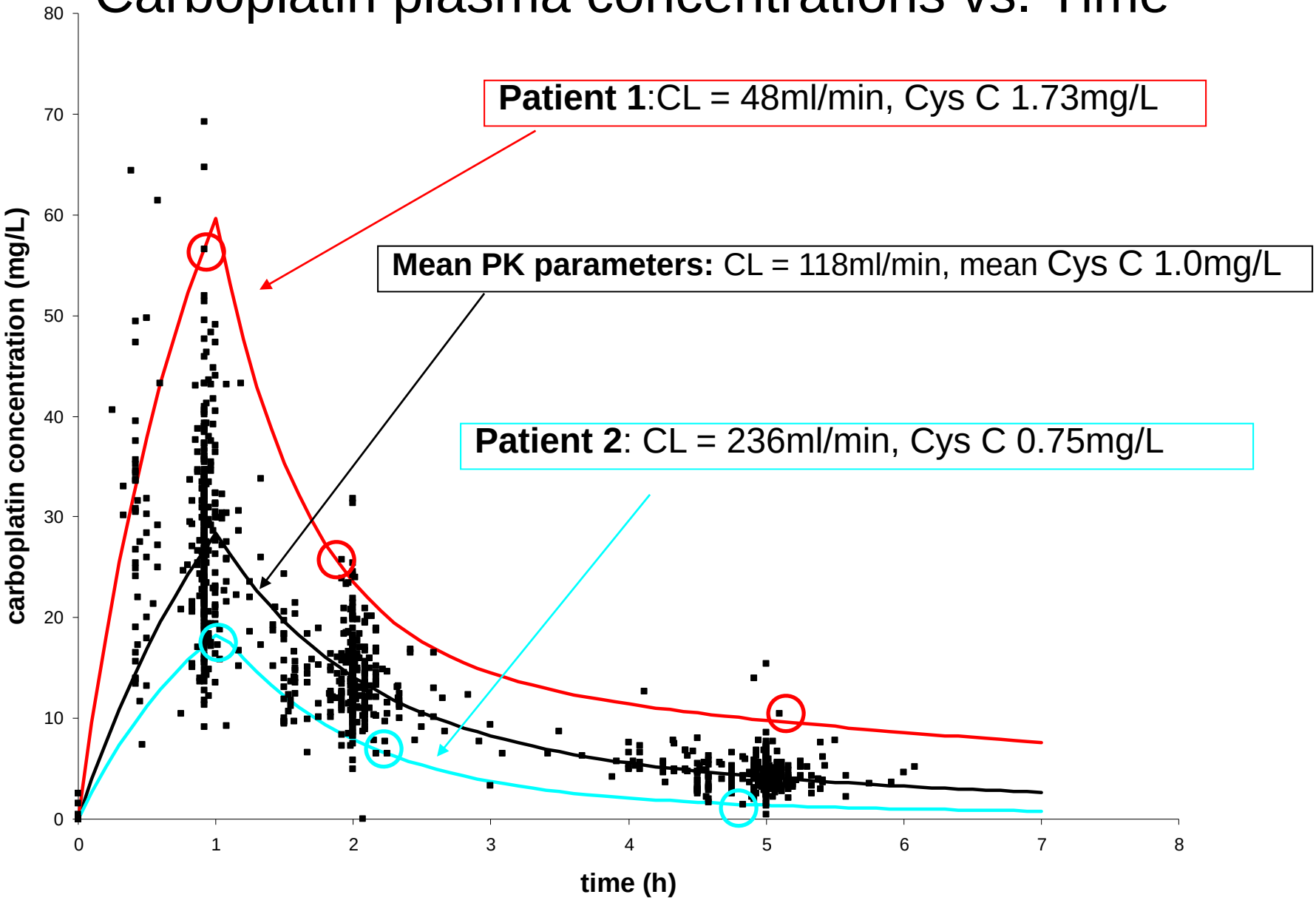
prospective validation [Clin Cancer Res 2009] of a first monocenter study (45 patients, Clin Pharmacokinet 2005)

- Multi-center study: 10 centres
- 357 patients, standard carboplatin treatment
- 3 blood samples per patient
- Population pharmacokinetic analysis
  - NONMEM program
  - Simultaneous analysis of data from all patients
  - Relationships between patients' characteristics (=covariates) and PK parameters

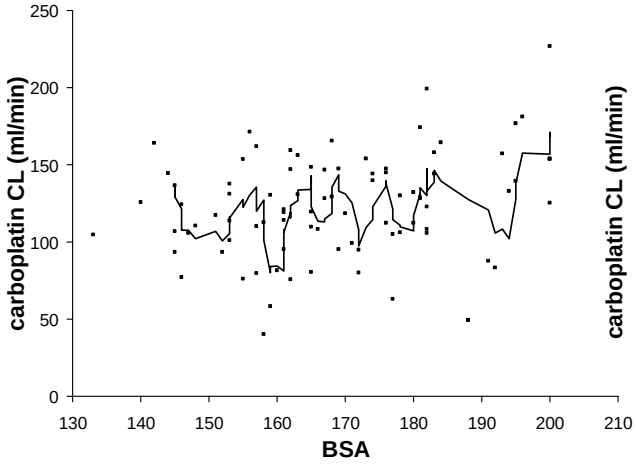
Carboplatin plasma concentrations vs. Time

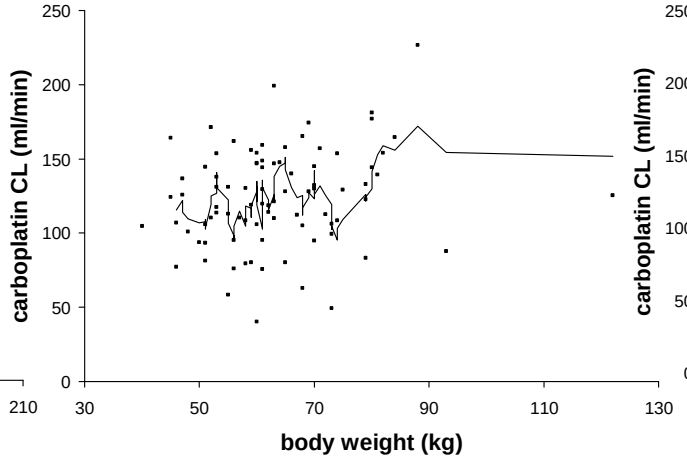


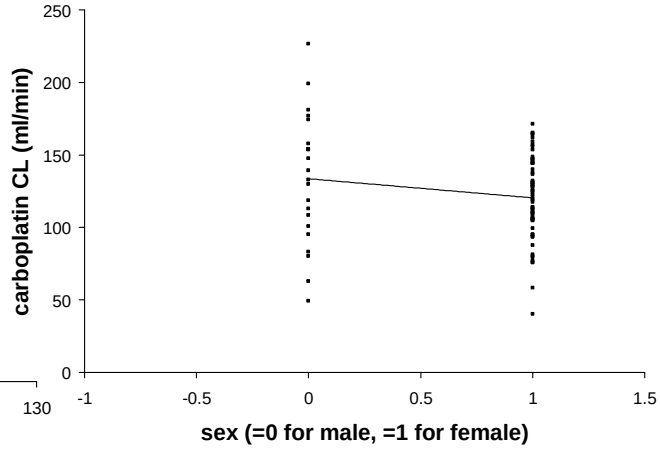
Carboplatin plasma concentrations vs. Time

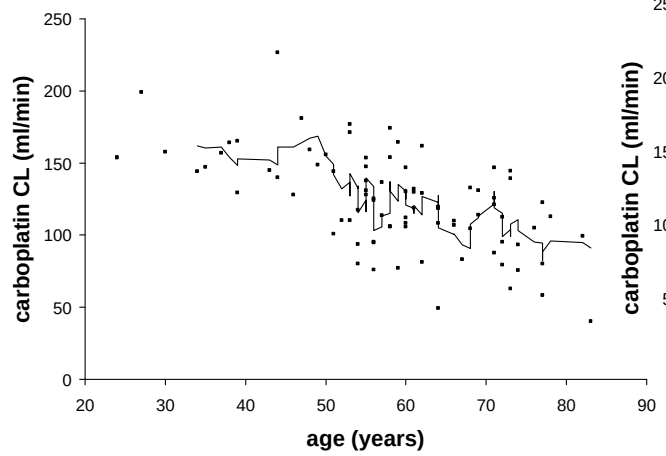


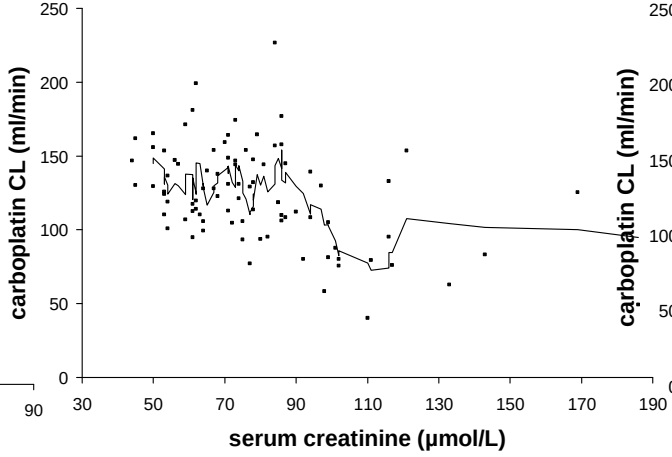
Carboplatin CL versus each characteristic

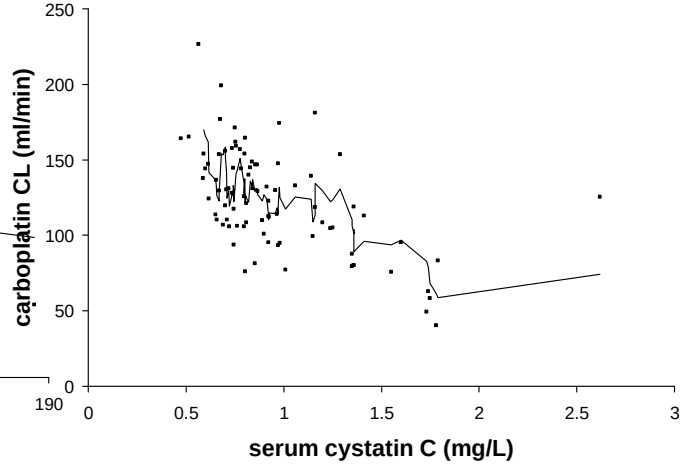












Best covariate equation to predict carboplatin CL

CL (mL/min) =

357 patients, multicentric study (modified Thomas formula):

$$118.\ (SCr/75)^{-0.450}.(cysC/1)^{-0.385}.(BW/65)^{0.504}.(AGE/56)^{-0.366}.\ 0.85^{SEX}$$

45 patients, monocentric study (original Thomas formula, Clin Pharmacokinet 2005):

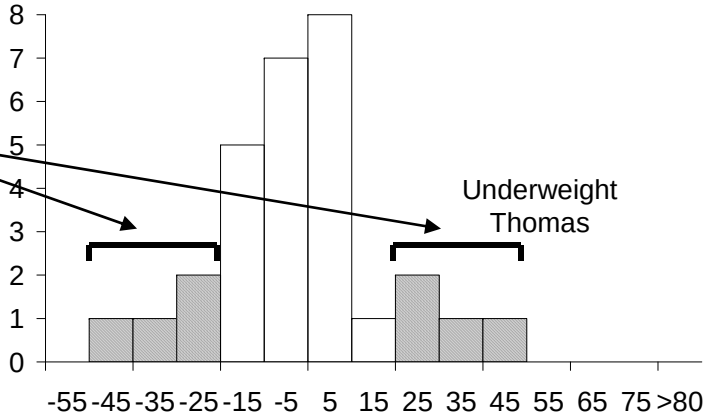
$$110.\ (SCr/75)^{-0.512}.(cysC/1)^{-0.327}.(BW/65)^{0.474}.(AGE/56)^{-0.387}.\ 0.85^{SEX}$$

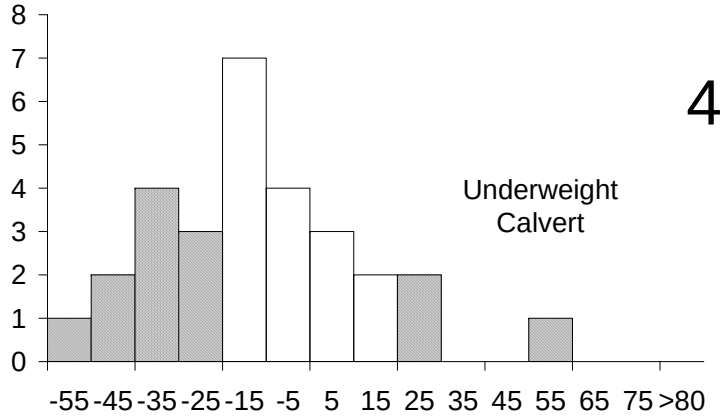
Evaluation of predictive performance in subgroups of patients defined according to their Body Mass Index:

Normal, Underweight (BMI<18.5), Obese (BMI>30)

percent error: (CLpred – CLobs)/CLobserved (x 100)

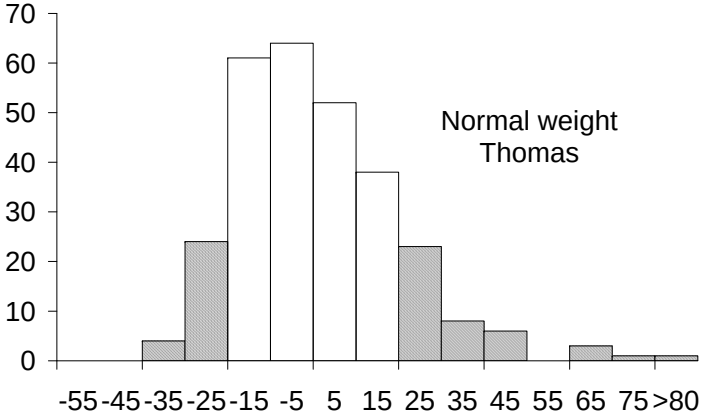
28%

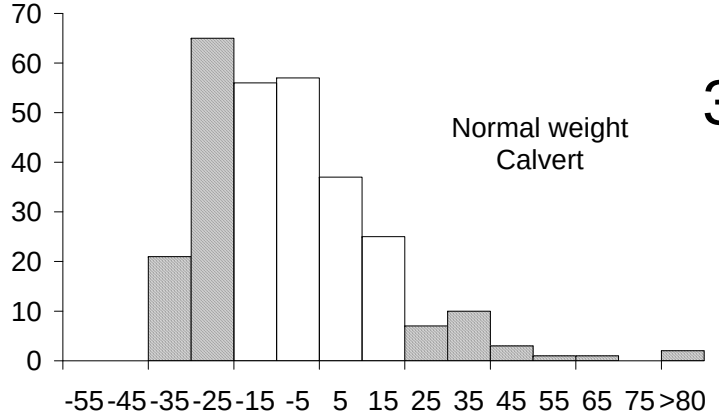




45%

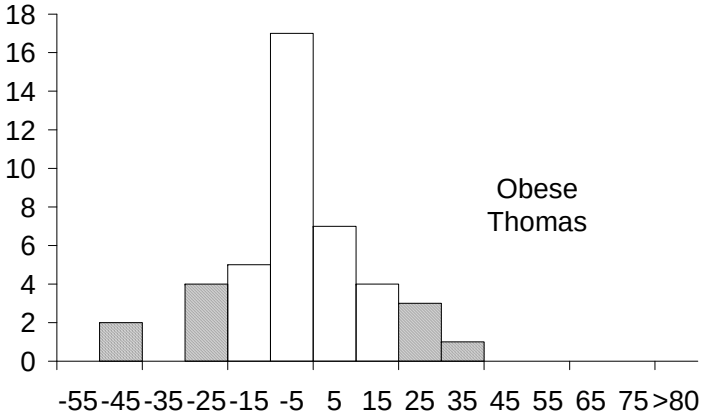
25%

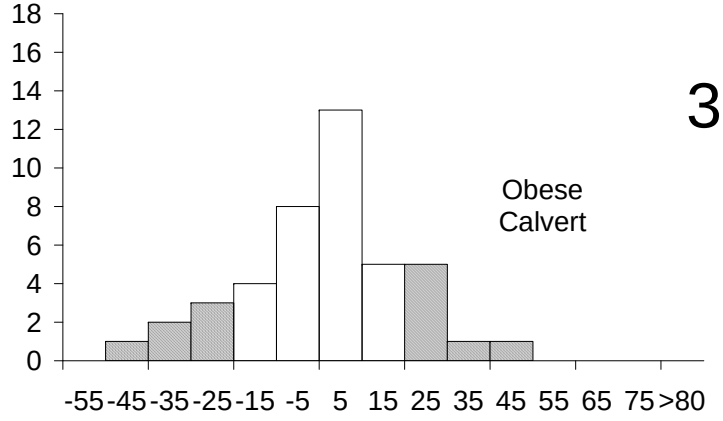




39%

23%





30%

Médicaments à élimination rénale importante

- Étoposide, topotécan, pemetrexed
- Valeur seuil de clairance de la créatinine
  - Pour contre-indiquer le médicament: pemetrexed (40 mL/min)
  - Pour adapter la posologie: topotecan (demi-dose si 20-40 mL/min)

Médicaments à élimination hépatique

- Docétaxel: fonctions hépatiques et CYP3A4 (ALAT, ASAT, PAL)
- Irinotécan: SN-38 et UDP-glucuronosyl-transférase UGT1A1 (*1 vs. *28): $(TA)_6TAA$ vs. $(TA)_7TAA$
- 5-fluoro-uracile et Dihydropyrimidine déshydrogénase (DPD)

ITKs: e.g., Imatinib

- Inhibitor of tyrosine kinase of Bcr-Abl (CML) and c-Kit (GIST)

- PK ; and corresponding variability
  - metabolized by CYP3A4 ; high IIV
  - substrat of ABCB1 (P-gp) ; additional PK variability
  - largely bound to α1-acid glycoprotein in plasma ; inflammatory protein, free fraction (fu) highly variable

- Dose is an issue: CML, GIST [reviewed by Jan Judson, J Clin Oncol 2008]

Imatinib and daily Dose (400mg, 600 mg), 2002

The New England Journal of Medicine

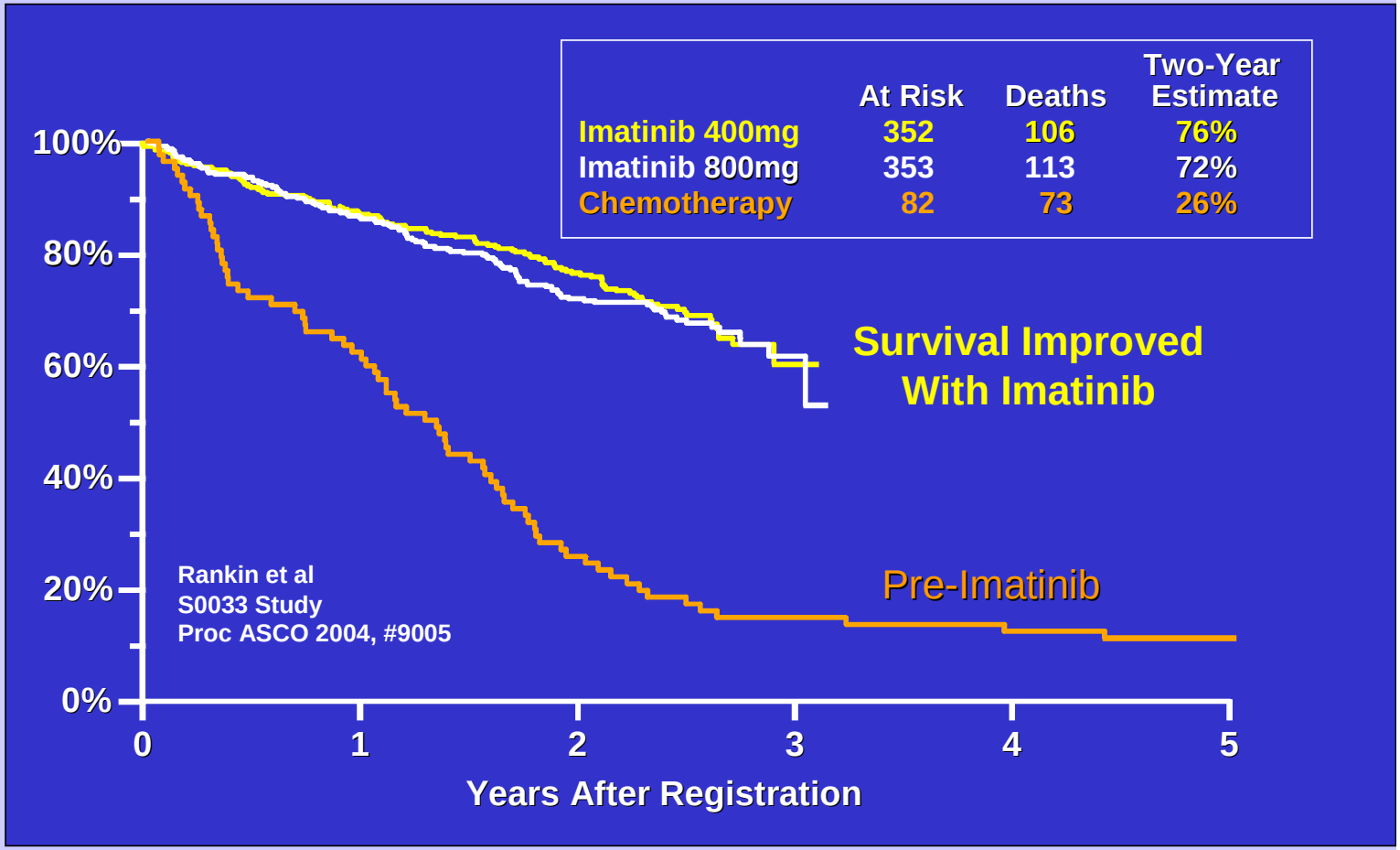
EFFICACY AND SAFETY OF IMATINIB MESYLATE IN ADVANCED GASTROINTESTINAL STROMAL TUMORS

GEORGE D. DEMETRI, M.D., MARGARET VON MEHREN, M.D., CHARLES D. BLANKE, M.D., ANNICK D. VAN DEN ABBEELE, M.D., BURTON EISENBERG, M.D., PETER J. ROBERTS, M.D., MICHAEL C. HEINRICH, M.D., DAVID A. TUVESON, M.D., PH.D., SAMUEL SINGER, M.D., MILOS JANICEK, M.D., PH.D., JONATHAN A. FLETCHER, M.D., STUART G. SILVERMAN, M.D., SANDRA L. SILBERMAN, M.D., PH.D., RENAUD CAPDEVILLE, M.D., BEATE KIESE, M.SC., BIN PENG, M.D., PH.D., SASA DIMITRIJEVIC, PH.D., BRIAN J. DRUKER, M.D., CHRISTOPHER CORLESS, M.D., CHRISTOPHER D.M. FLETCHER, M.D., AND HEIKKI JOENSUU, M.D.

occurred in approximately 5 percent of patients. There were no significant differences in toxic effects or response between the two doses. Imatinib was well ab-

Confirmed for 400 mg vs. 800 mg [Rankin et al, ASCO 2004]

Imatinib & Overall Survival in metastatic GIST

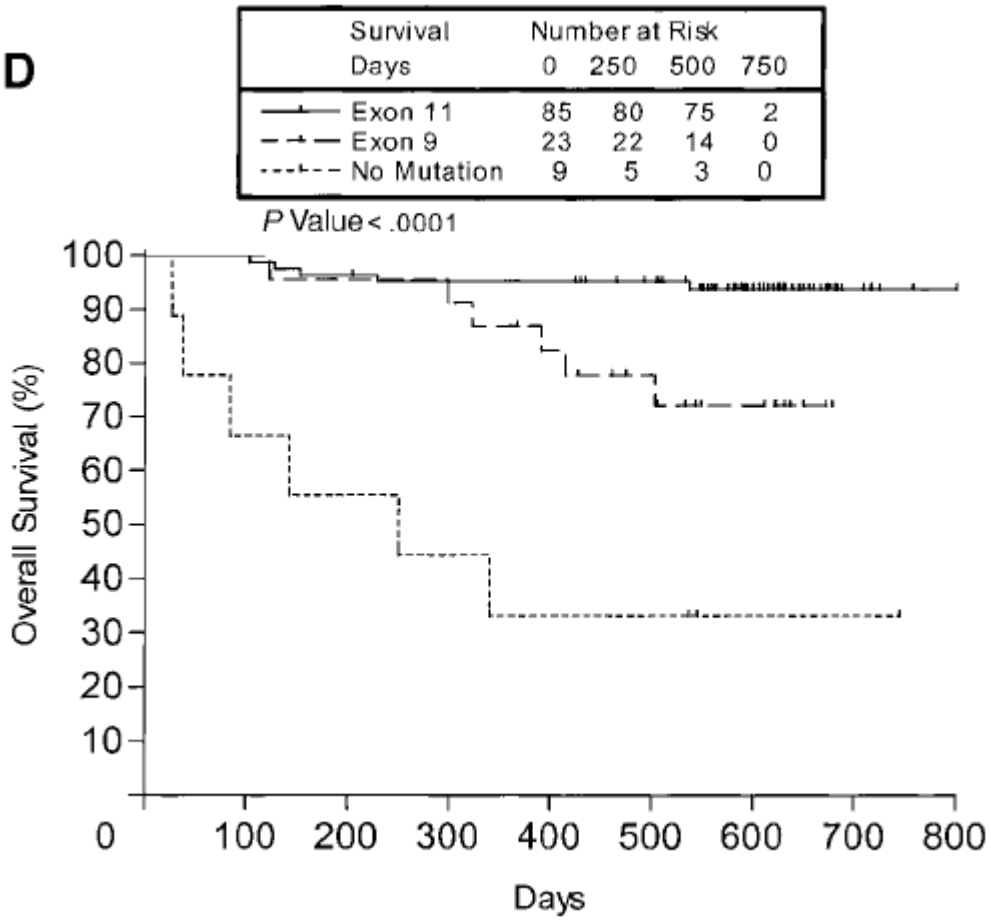


Efficacy is highly dependent of Kit genotype

Kinase Mutations and Imatinib Response in Patients With Metastatic Gastrointestinal Stromal Tumor

By Michael C. Heinrich, Christopher L. Corless, George D. Demetri, Charles D. Blanke, Margaret von Mehren, Heikki Joensuu, Laura S. McGreevey, Chang-Jie Chen, Annick D. Van den Abbeele, Brian J. Druker, Beate Kiese, Burton Eisenberg, Peter J. Roberts, Samuel Singer, Christopher D.M. Fletcher, Sandra Silberman, Sasa Dimitrijevic, and Jonathan A. Fletcher

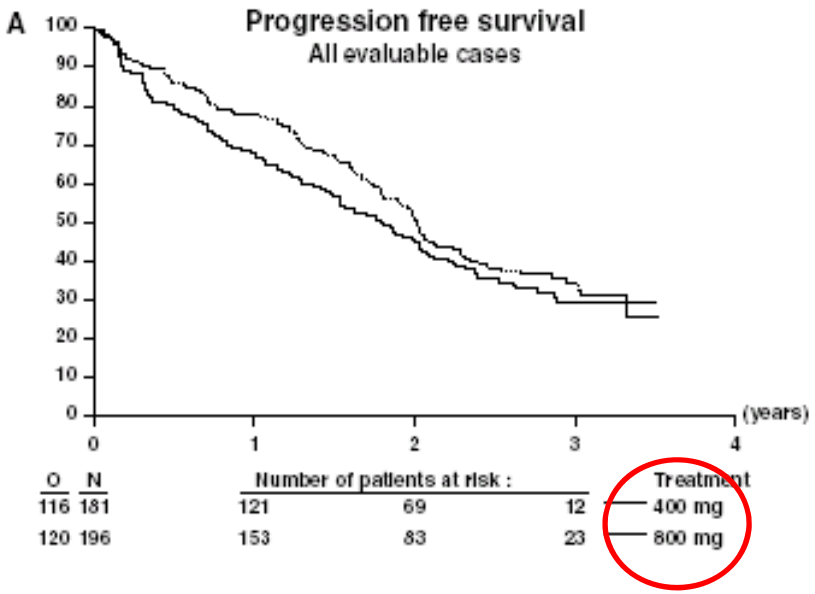
J Clin Oncol 2003

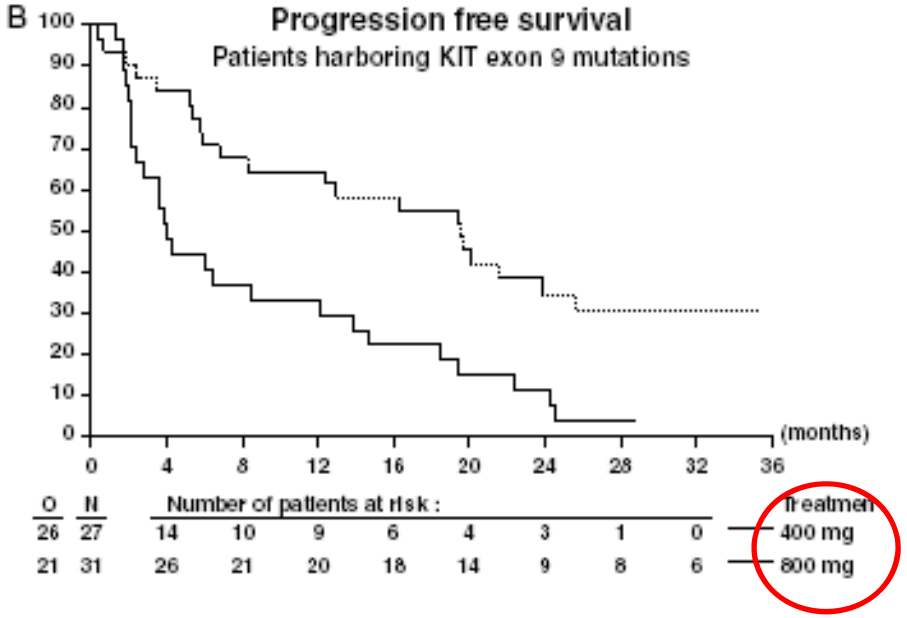


KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours

Eur J Cancer 2006

Maria Debiec-Rychter[a,], Raf Sciot[b], Axel Le Cesne[d], Marcus Schlemmer[e], Peter Hohenberger[f], Allan T. van Oosterom[c], Jean-Yves Blay[g], Serge Leyvraz[h], Michel Stul[a], Paolo G. Casali[i], John Zalcberg[j], Jaap Verweij[k], Martine Van Glabbeke[l], Anne Hagemeijer[a], Ian Judson[m], On behalf of the EORTC Soft Tissue and Bone Sarcoma Group, The Italian Sarcoma Group and the Australasian GastroIntestinal Trials Group*



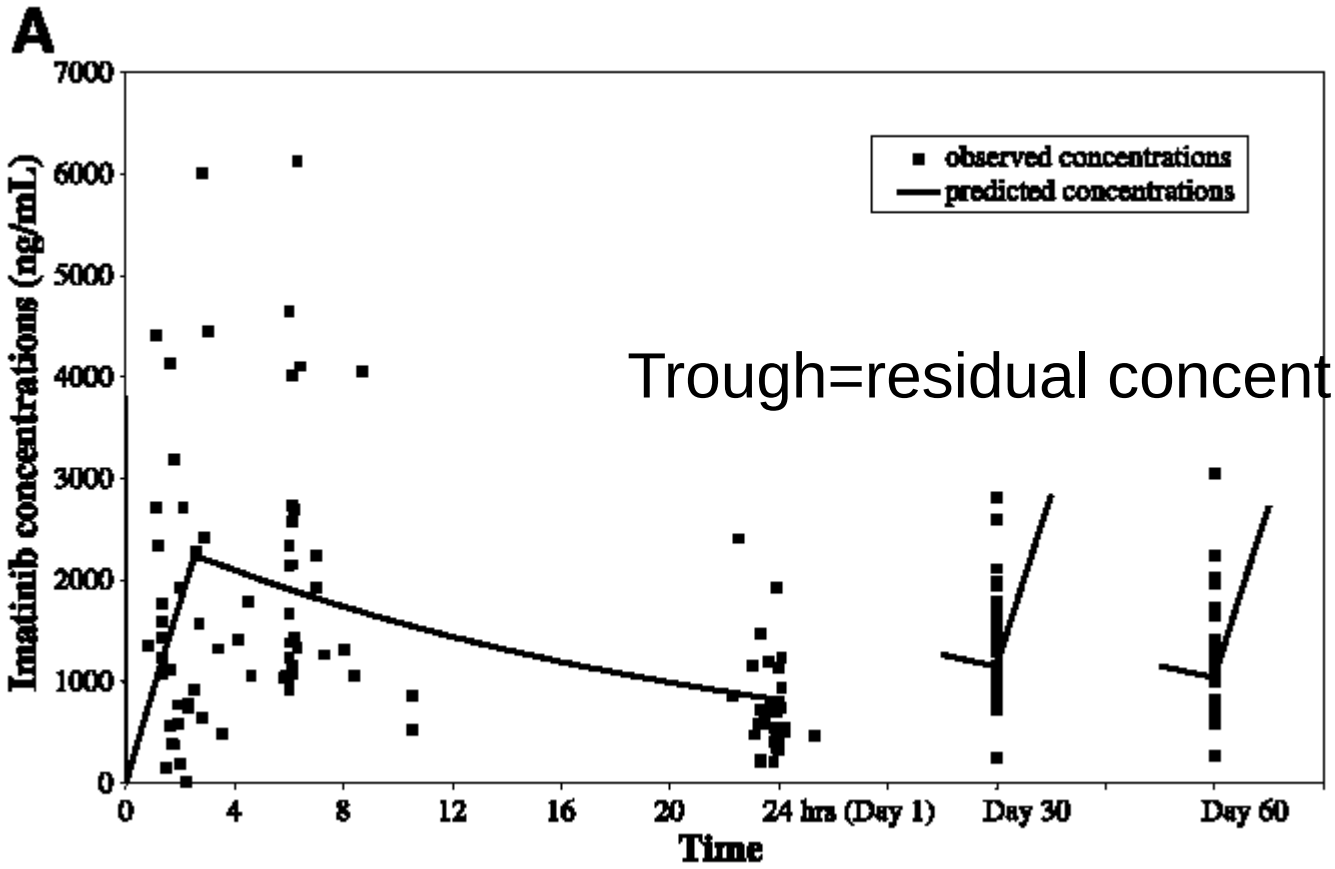


Dose is (in fact) an issue ; what about the concentrations ?

Pharmacokinetic-Pharmacodynamic Relationships of Imatinib and Its Main Metabolite in Patients with Advanced Gastrointestinal Stromal Tumors

Catherine Delbaldo,[1] Etienne Chatelut,[2] Micheline Ré,[3] Alain Deroussent,[4] Sophie Séronie-Vivien,[2] Aurore Jambu,[2] Patrice Berthaud,[6] Axel Le Cesne,[5] Jean-Yves Blay,[7] and Gilles Vassal[3]

Clin Cancer Res 2006

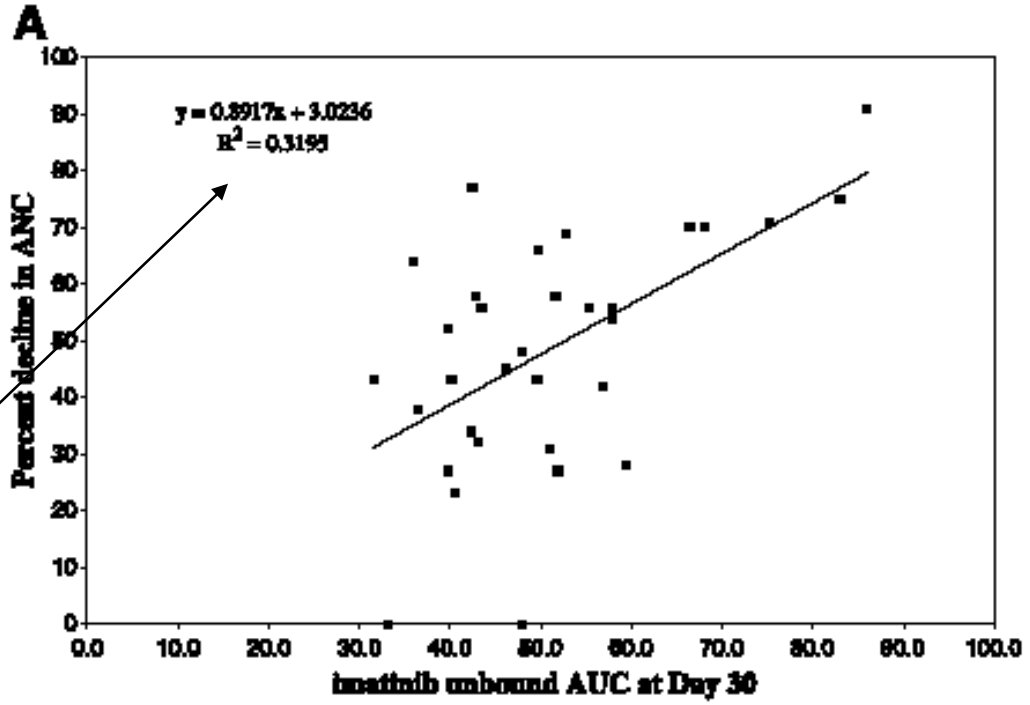


Trough=residual concentrations

Relationship between daily AUC and hematopietic toxicity

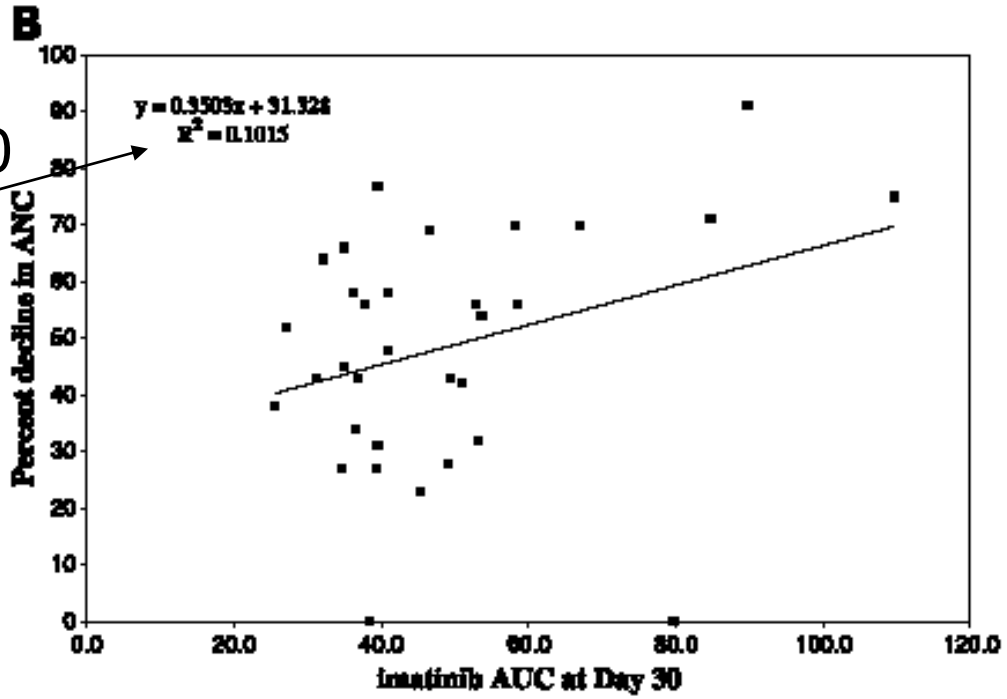
R^2=0.32

Free plasma imatinib concentrations (unbound AUC estimated from α1-glycoprotein acid



R^2=0.10

Total plasma imatinib concentrations (AUC)



Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia

Stephane Picard,[1,2,3] Karine Titier,[1,2,3] Gabriel Etienne,[4] Emmanuelle Teilhet,[1,2,3] Dominique Ducint,[1,2,3] Marie-Agnes Bernard,[1] Regis Lassalle,[1] Gerald Marit,[2,5,6] Josy Reiffers,[4] Bernard Begaud,[1,2,3] Nicholas Moore,[1,2,3] Mathieu Molimard,[1,2,3] and Francois-Xavier Mahon[2,5,6]

Blood 2007

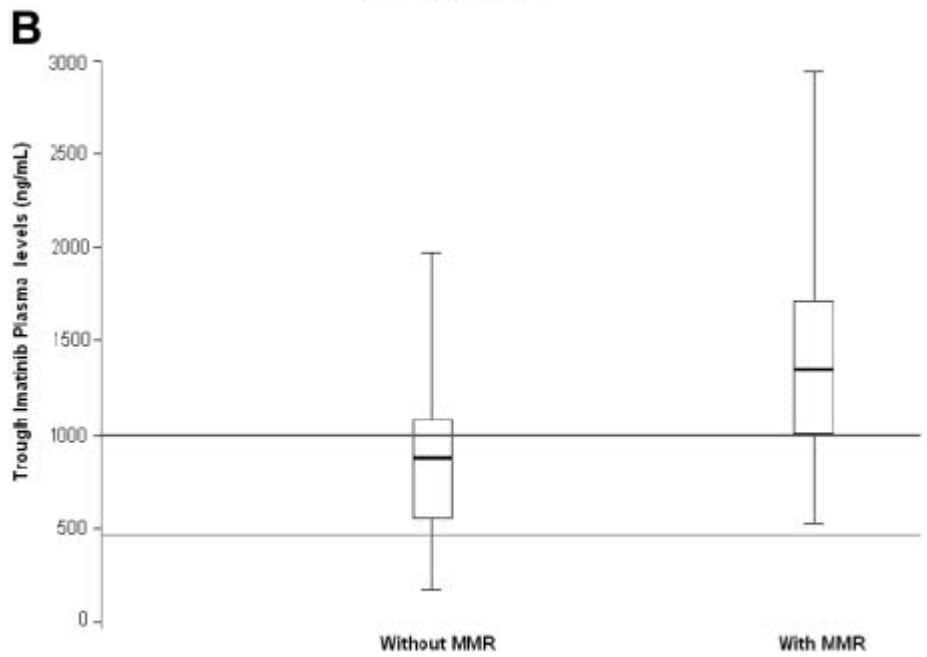


Figure 1. Trough plasma imatinib threshold for major molecular response (MMR).(A) Receiver operating characteristic (ROC) curve analysis. Regarding

Relationship of imatinib-free plasma levels and target genotype with efficacy and tolerability

N Widmer*[,1], LA Decosterd[1], S Leyvraz[2], MA Duchosal[3], A Rosselet[3], M Debiec-Rychter[4], C Csajka[1], J Biollaz[1] and T Buclin[1]

Unbound AUC

BJC 2008

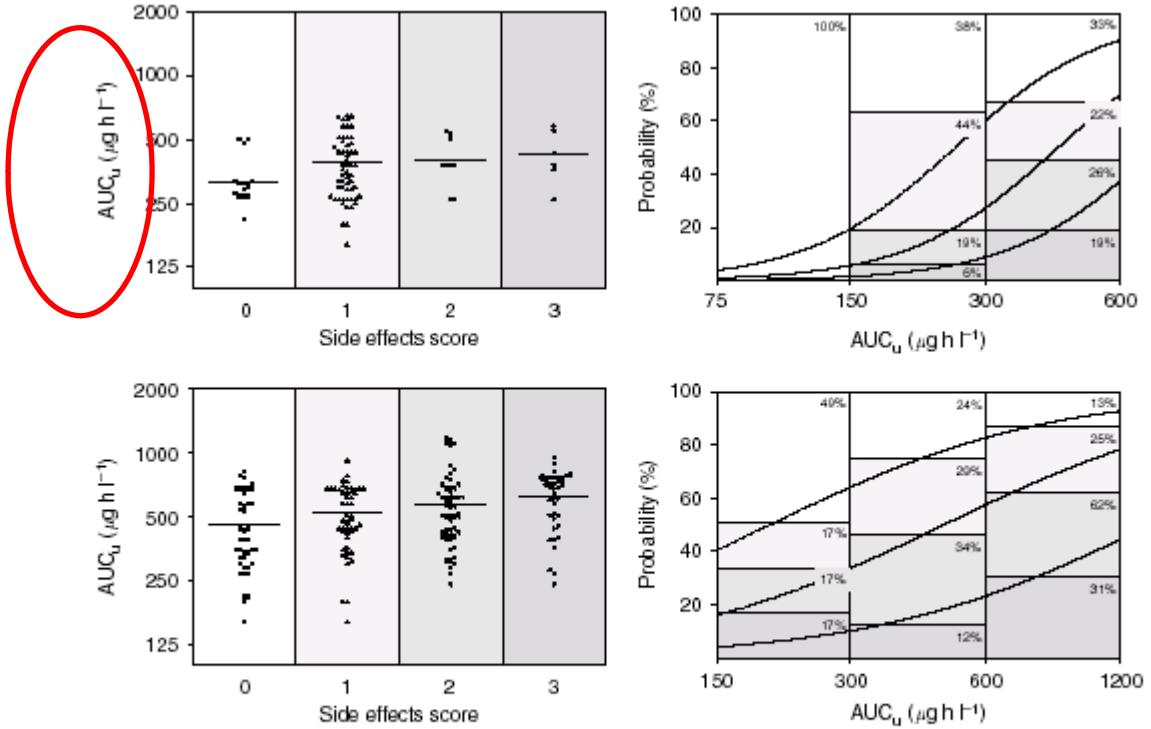
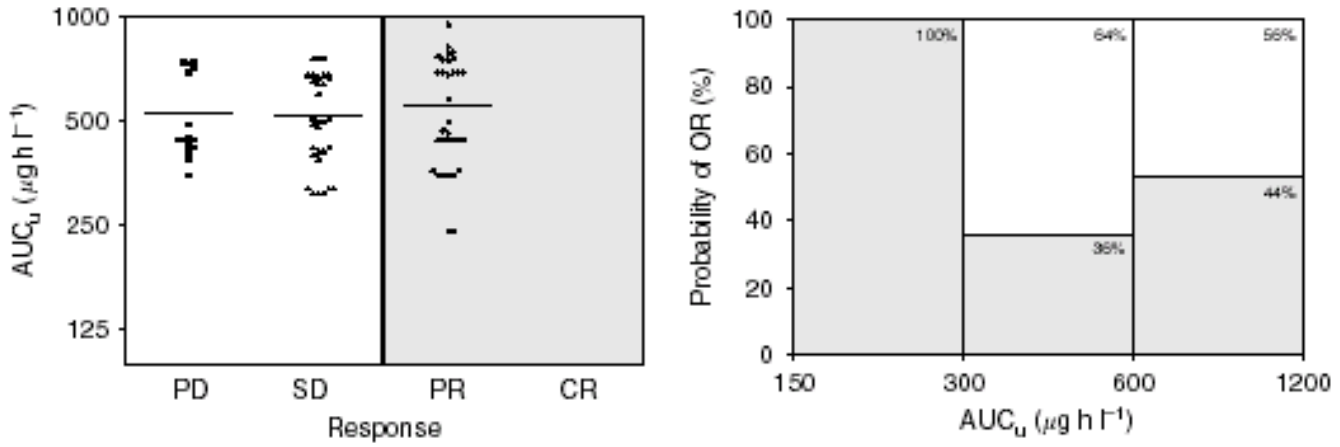


Figure 1 Relationship between free drug exposure (AUC_u) and toxicity in CML (upper part) and GIST patients (lower part). Left panel: scatter plot of AUC_u according to side effects score (0 = no side effects, 1 = 1 side effect, 2 = 2 side effects and 3 = 3 or more side effects). Right panel: probability of side effects according to the per-sample PK–PD analyses. The histograms represent the percentages observed for the three types of response at three typical AUC_u range values (side effects score: white box = 0; light grey box = 1; grey box = 2; dark grey box = 3). The curves, modelled by a four-level ordered logistic regression, show the probability of side effects according to AUC_u.

Relationship of imatinib-free plasma levels and target genotype with efficacy and tolerability

N Widmer*[,1], LA Decosterd[1], S Leyvraz[2], MA Duchosal[3], A Rosselet[3], M Debiec-Rychter[4], C Csajka[1], J Biollaz[1] and T Buclin[1]

Exon 11



Exon 9

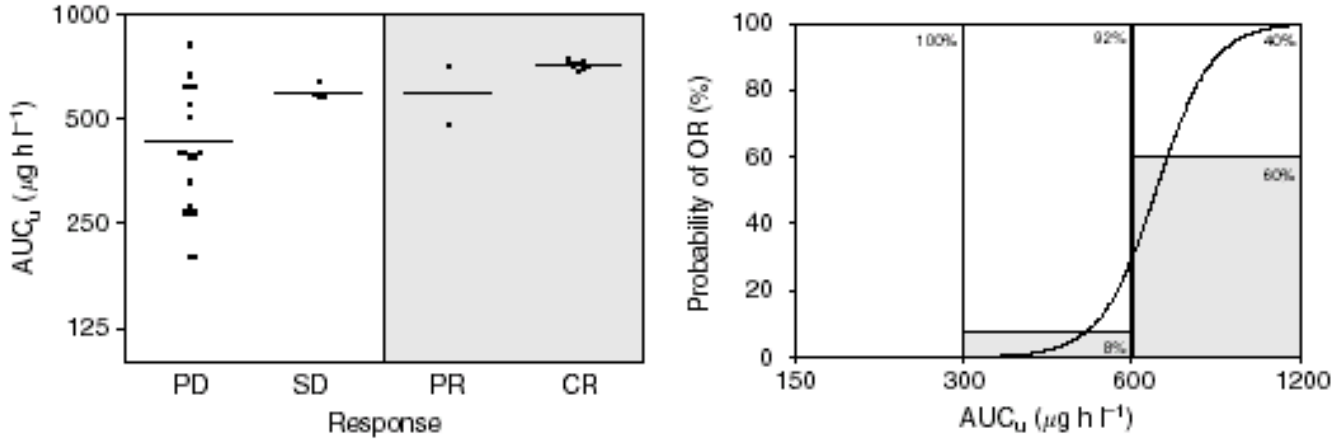


Figure 2 Relationship between free drug exposure (AUC_u) and response in GIST patients. Upper part: exon 11 *KIT* genotype; lower part: exon 9 or wt *KIT* genotype. Left panel: scatter plot of AUC_u according to RECIST score; white box = PD + SD (score 0; $n = 23$ for exon 9/wt, 46 for exon 11); grey box = OR, OR = CR + PR (score 1; $n = 10$ for exon 9/wt, 32 for exon 11). Right panel: probability of response according to the per-sample PK–PD analysis for both main genotypes of GIST patients. The histograms represent the percentages observed for the two types of response at three typical AUC_u range values. The curve, modelled by a two-level ordered logistic regression, shows the probability of response according to AUC_u.

Imatinib Plasma Levels Are Correlated With Clinical Benefit in Patients With Unresectable/Metastatic Gastrointestinal Stromal Tumors

J Clin Oncol 2009

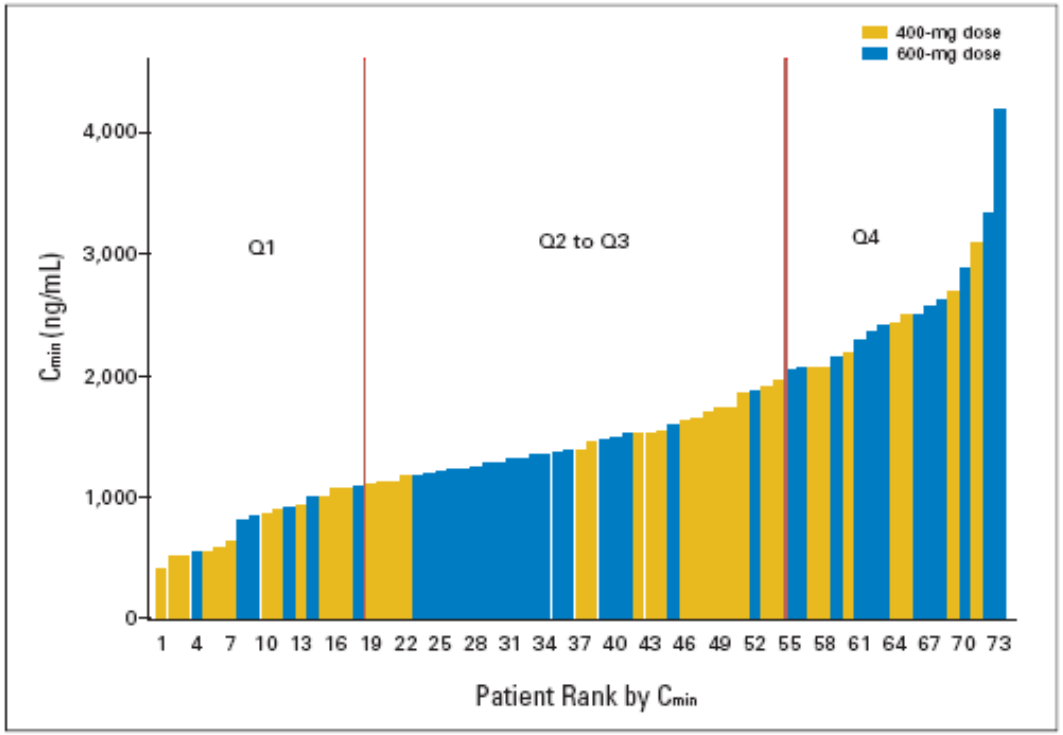


Fig 2. Distribution of imatinib trough concentration (C_{min}) at steady-state (day 29) for 400-mg and 600-mg daily doses combined. For the 36 patients in the 400-mg dose group, 12 patients were in quartile 1 (Q1), 17 were in Q2-Q3, and seven were in Q4, whereas for the 37 patients in the 600-mg dose group, six were in Q1, 19 were in Q2-Q3, and 12 were in Q4. The vertical lines represent 25% and 75% percentiles (ie, 1,100 and 2,040 ng/mL), respectively, dividing the population into three groups: Q1 (414 to 1,110 ng/mL; n = 18), Q2-Q3 (1,110 to 2,040 ng/mL; n = 36), and Q4 (2,041 to 4,182 ng/mL; n = 19).

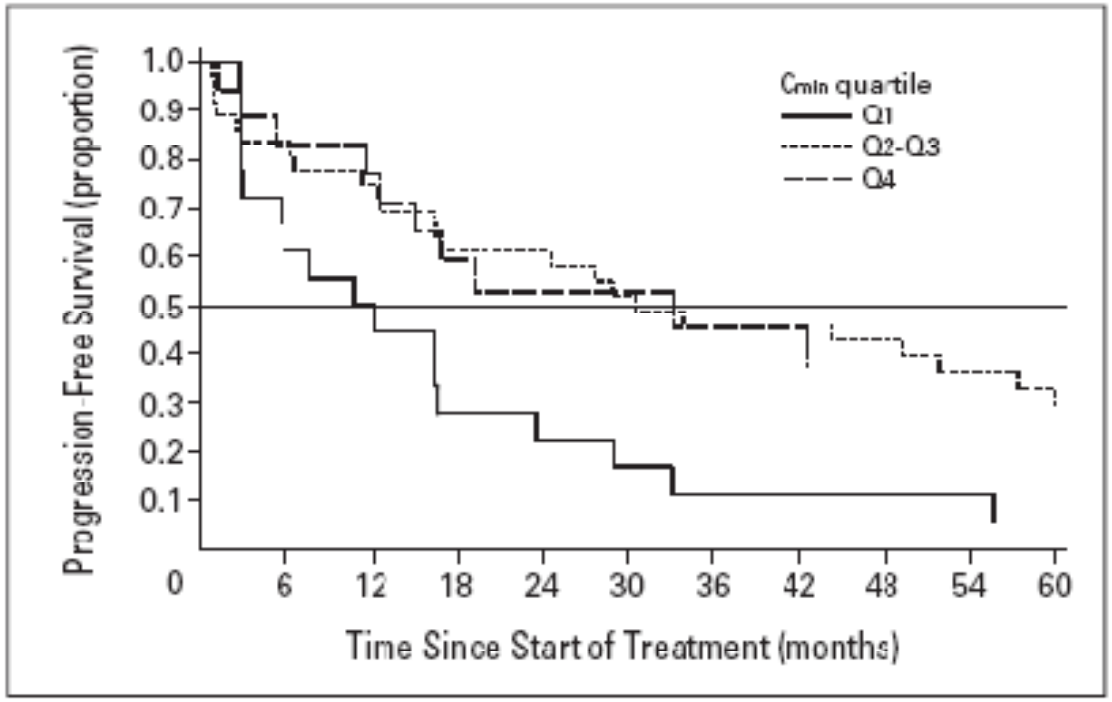
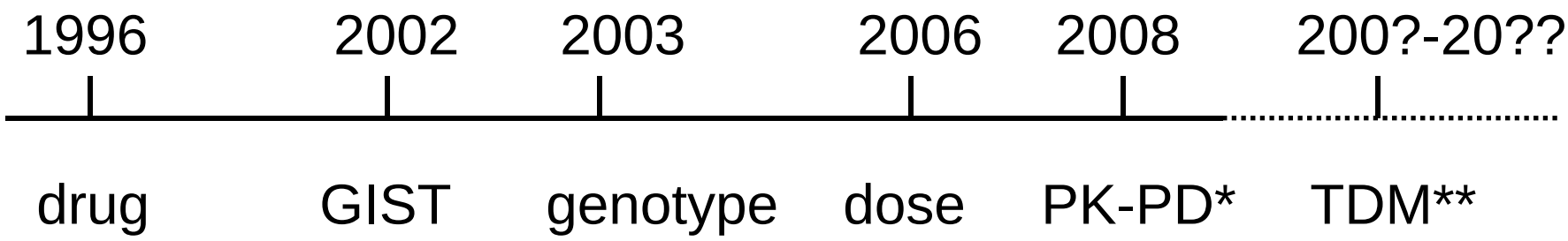


Fig 3. Time to progression by imatinib day 29 trough level (C_{min}) quartile (Q).

Historic of Imatinib and GIST



*PK-PD relationships

** Therapeutic Drug monitoring

TDM et Hautes Doses

TICE: taxol, ifosfamide, carboplatin, etoposide

[Motzer et al, J Clin Oncol 2000]

phase I: niveau d'AUC de carboplatine de 12 à 32 mg/mL x min (AUC totale correspondant à 3 perfusion quodienne par cycle)

phase II: AUC optimale de 24 mg/mL x min

Dose = (DFG + 25) x 24

Où DFG prédit par l'équation de Calvert-Jelliffe

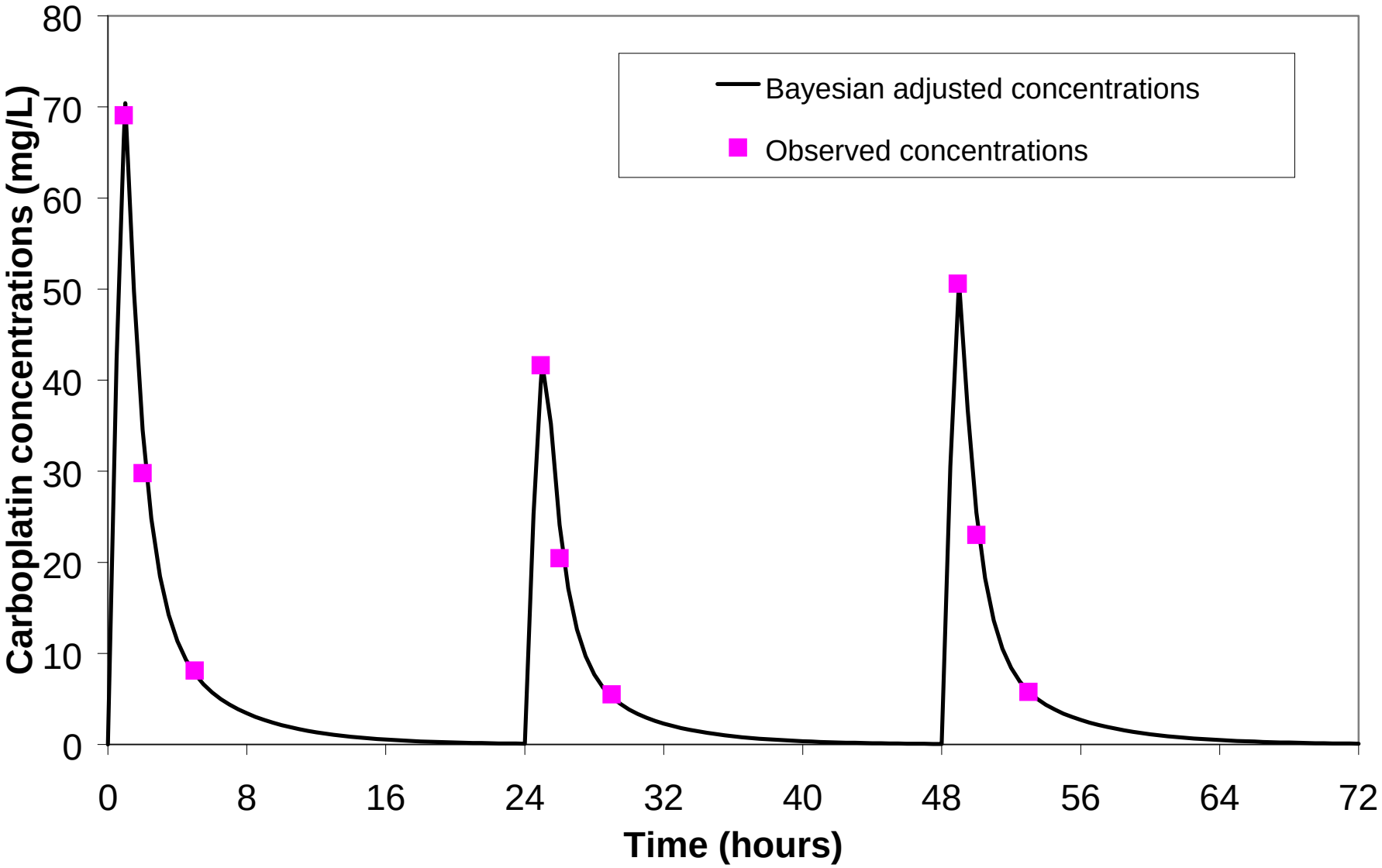
Limite de la méthode d'adaptation a priori

Table 4. Target AUC and Measured AUC per Dose Level With Carboplatin (n = 37)

Target AUC [(mg/ml)·min]	No. of Patients*	Measured AUC [(mg/ml)·min]		Ratio of Target to Measured AUC	
		Mean	Range	Mean	Range
21	8	17.4	11.4-31.4	1.3	0.7-1.8
24	26	21.6	10.9-36.7	1.2	0.7-2.2
28	3	33	26.2-44.0	0.89	0.6-1.1

Abbreviation: AUC, area under the curve.
*Ten of 47 patients are not included here (three did not receive high dose, and seven did not undergo pharmacokinetic studies).

E.g., Observed AUC 24.8 (vs. 30.9 sans adaptation de dose)



Ototoxicity of High-Dose Carboplatin

J Clin Oncol 2005

Christine Chevreau, Fabienne Thomas, Corinne Couteau, Florence Dalenc, Loic Mourey, and Etienne Chatelut
Institut Claudius-Regaud, Toulouse, France

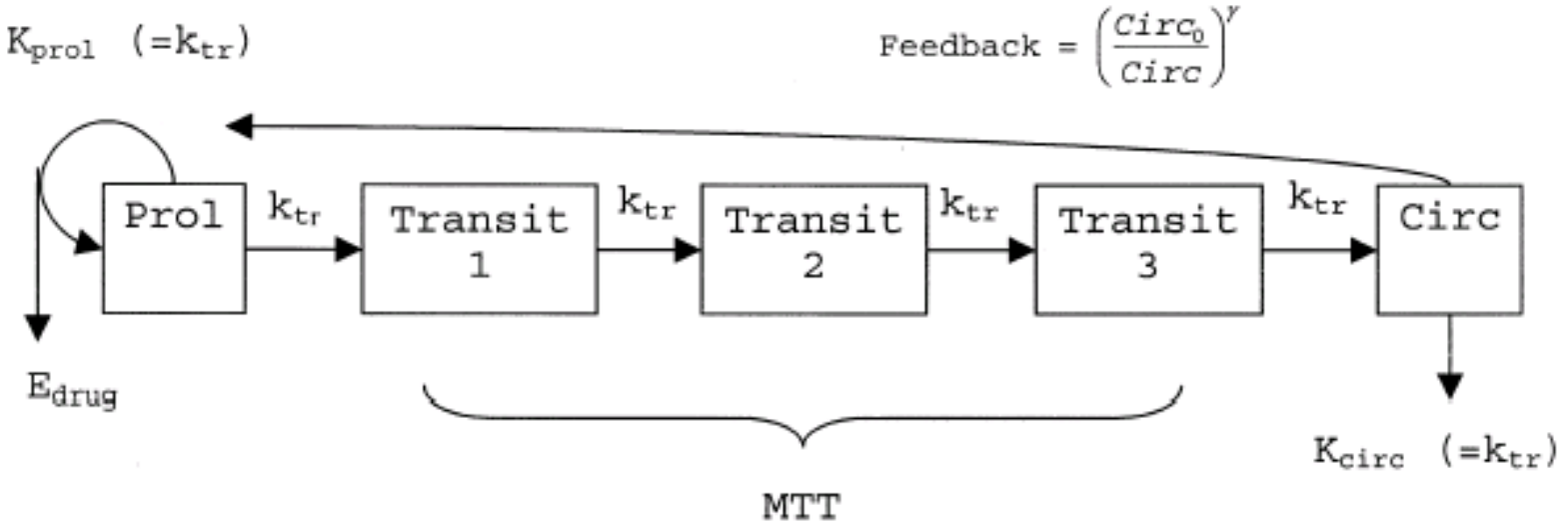
Table 1. Patients' Carboplatin Pharmacokinetic Parameters, Treatment, and Toxicity

Patient	Previous Cisplatin Dose (mg/m^2)	Cycle	Target Total AUC (mg/mL × min)	Predicted CL* (mL/min)	Mean Observed CL		Observed Total AUC (mg/mL × min)	Total Dose (mg)	Neuro-Oric Common Toxicity Criteria
					mL/min	CV%			
1	400	1	24	181	150	6	25.0	3,750	2
		2	24	162	121	8	26.5	3,210	
		3	16	130	111	NE	NE	1,805	
2	400	1	24	226	142	5	24.8	3,500	NE
		2	24	174	121	2	24.1	2,940	
3	400	1	24	126	66	26	24.0	1,595	3
		2	24	116	84	15	25.1	2,145	
4	700	1	24	188	127	9	25.0	3,230	3
		2	24	162	126	12	25.7	3,180	
		3	8	179	139	0	7.1	990	
5	200	1	24	238	191	3	24.2	4,620	3
		2	24	255	193	8	24.4	4,650	
		3	16	246	174	3	16.0	2,780	

Abbreviations: AUC, area under the curve; CL, clearance; CV%, coefficient of variation for interday variability; NE, not assessable.
*Carboplatin clearance predicted according to the Chatelut formula.

Modèle PK-PD

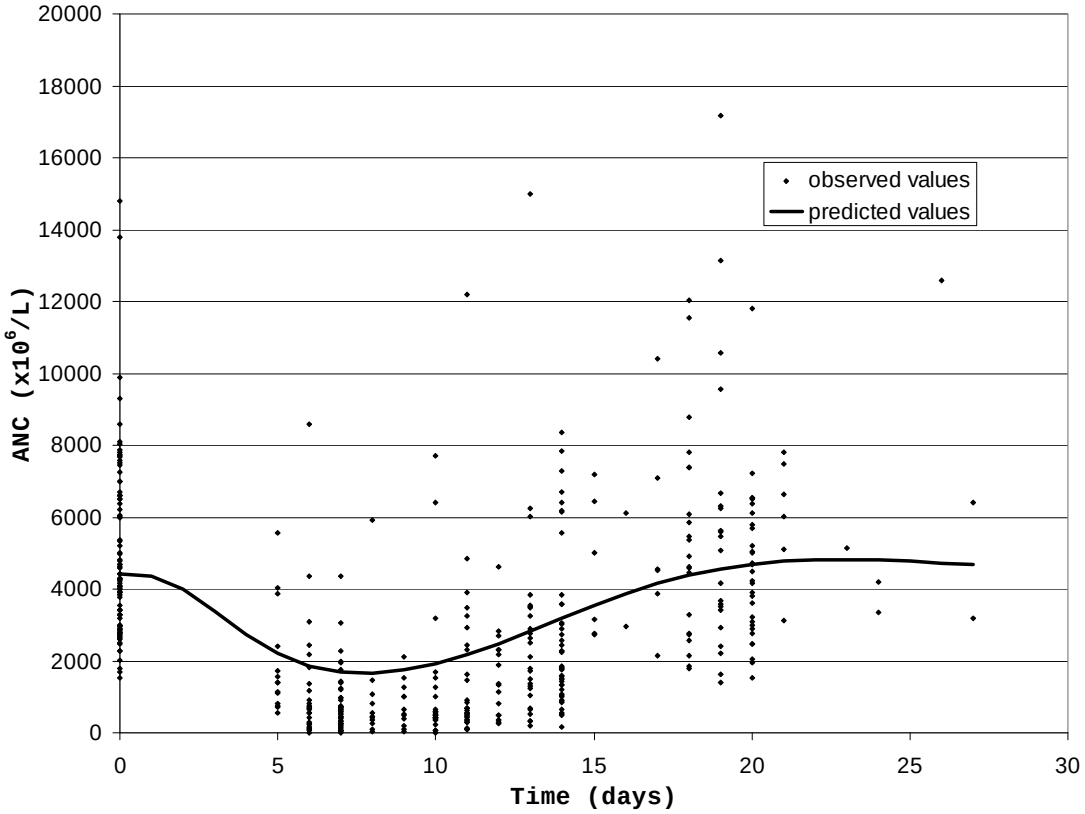
[Friberg et al, J Clin Oncol 2002]



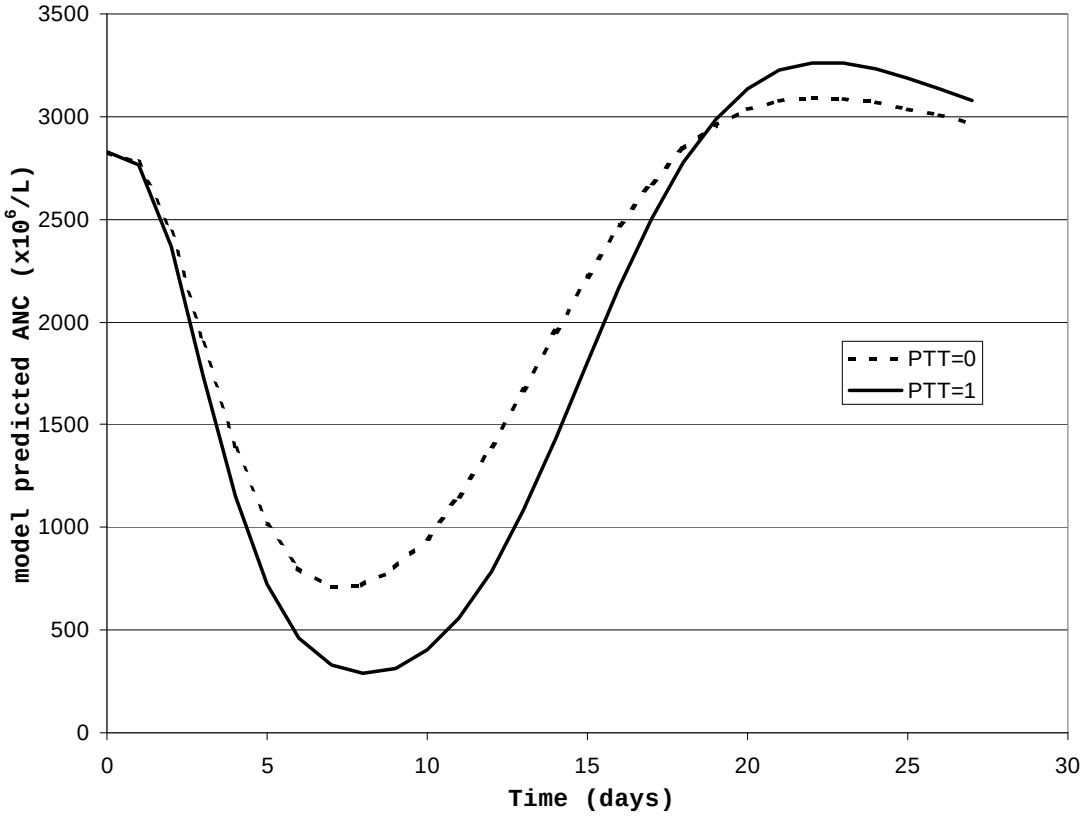
À tout instant t:

$E_{drug} = K_{sens}$ x Conc plasma du cytotoxique

Docétaxel et neutropénie
[Puisset et al, Br J Cancer 2007]



Neutropénie vs. Pré-traitement



Conclusion

- More drug is better even of targeted therapy
- More individual information is needed to perform optimal treatment: e.g. inib
  - disease (is any TK receptor involved ?)
  - genotype (tumour of the patient)
  - PK (patient): trough concentrations, AUC, AUCu (free AUC)
- Standardisation des Protocole d’adaptation individuelle des doses

EORTC-PAMM meeting

Toulouse January 28-30 2010

main topic: Treatment individualization

http://www.eortc-pamm2010-toulouse.fr/accueil.htm