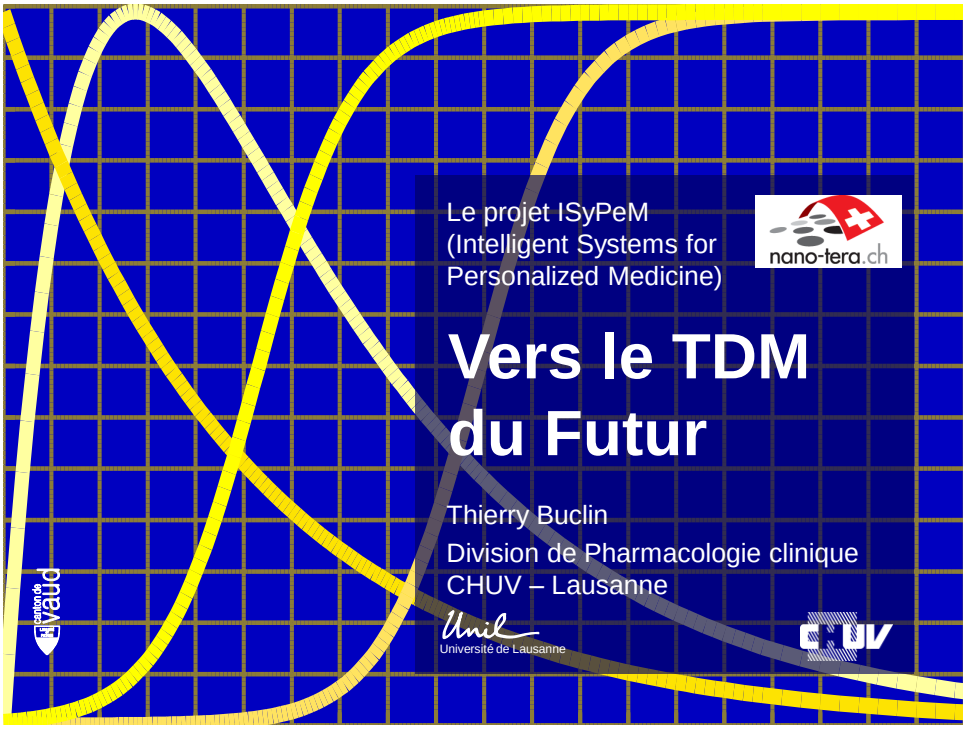


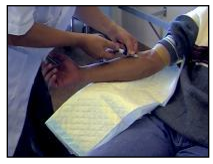
Limitations du TDM actuel

- **Empirisme prévalent** dans le monitoring et l'ajustement posologique (rares exceptions au fétichisme de la dose : trop de mesures et pas assez d'interprétation,)
- **Cadre conceptuel lacunaire** pour élaborer un monitoring rationnel (indices de performances)
- **Manque d'études contrôlées**, mauvaise acceptation par les prescripteurs (aspects éthiques et pratiques)
- **Recherche peu soutenue** tant par l'industrie que les organismes publics (divergence d'intérêt)
- **Manque d'incitation** des autorités d'enregistrement
- **Difficultés pratiques** pour réaliser un TDM efficient (prélèvement, envoi, analyse, interprétation, application)

TDM : Procédures actuelles

Information
+ Traitement

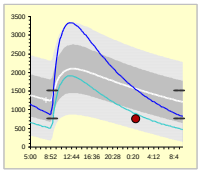
Demande de TDM
+ Données cliniques



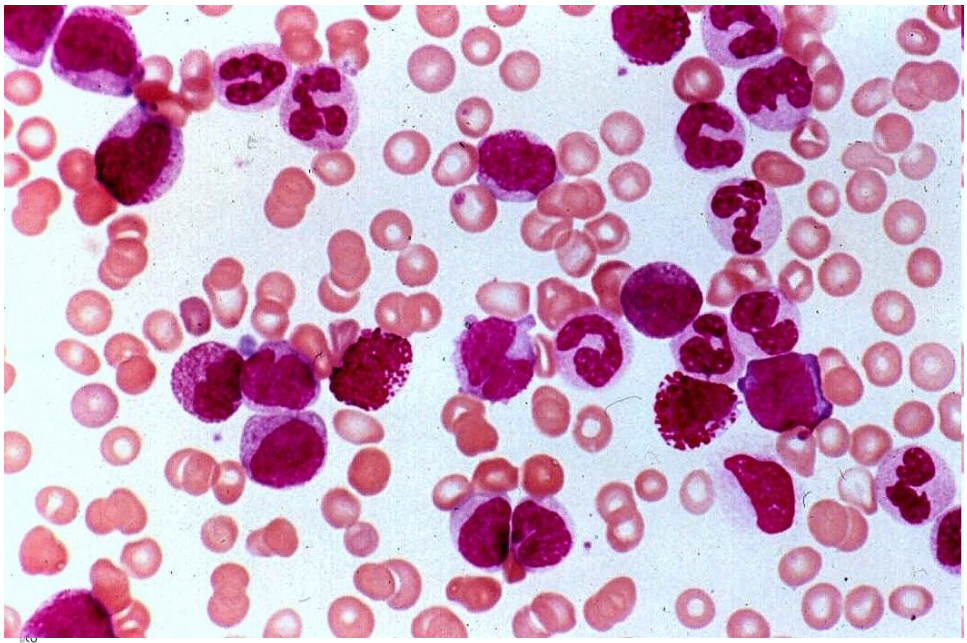
Prise de sang

Envoi au laboratoire

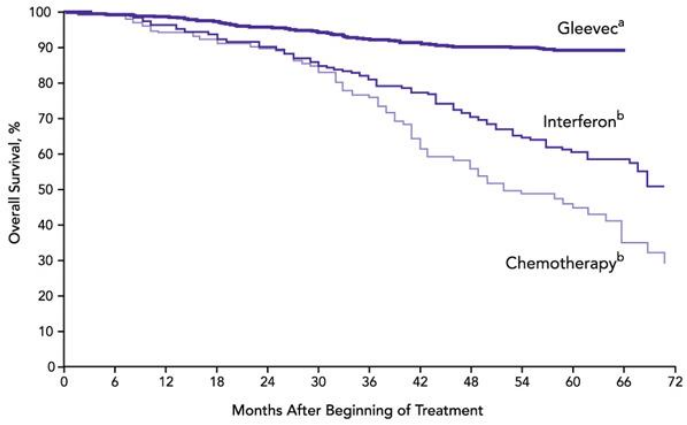
Analyse



Interprétation
+ Recommendations

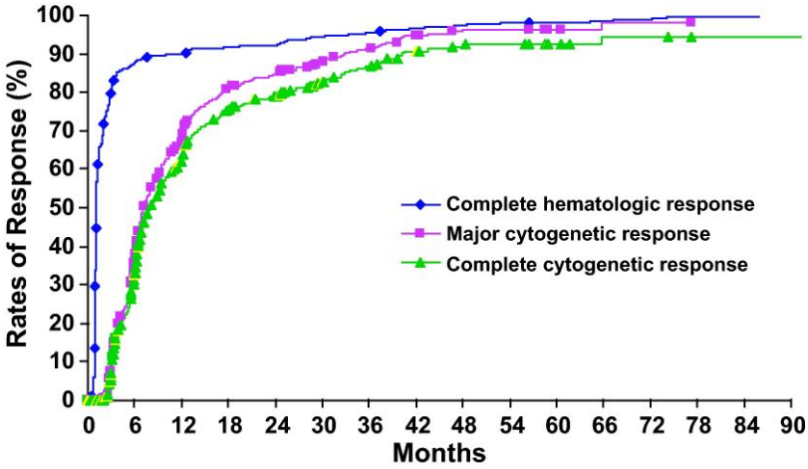


Imatinib dans la LMC



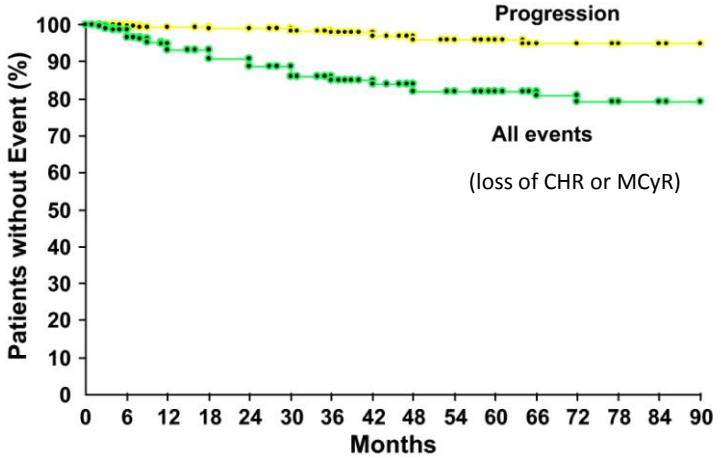
[a] From Druker BJ, Guilhot F, O'Brien SG *et al. N Engl J Med.* (2006) **355**:2408-2417.
[b] From The Italian Cooperative Study Group On Chronic Myeloid Leukemia. *N Engl J Med.* (1994) **330**:820-825.

Progression vers la rémission complète



Tauchi T & al. Seven-year follow-up of patients receiving imatinib…
Leuk Res. 2011 35(5):585-90

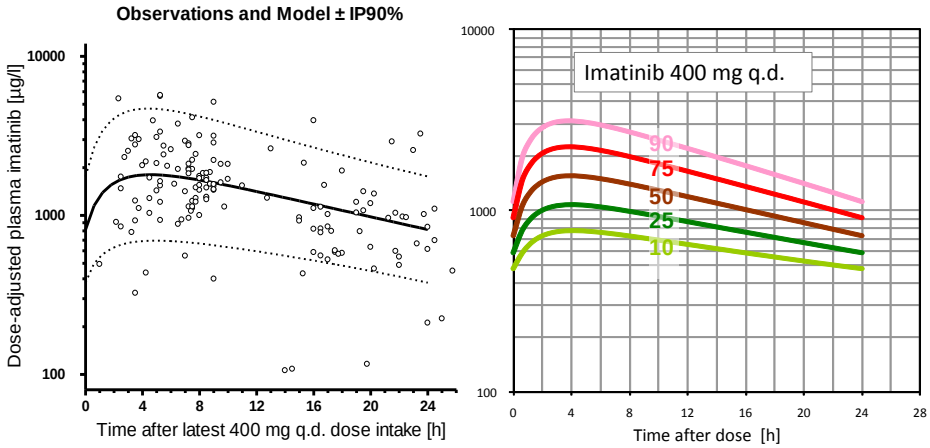
Encore des échappements malgré tout



Tauchi T & al. Seven-year follow-up of patients receiving imatinib…
Leuk Res. 2011 35(5):585-90

L'imatinib a une forte variabilité PK

Percentiles de l'étude de PK de population lausannoise 2006 (50 patients CML et GIST) :



Widmer N, Buclin T et al. Br J Clin Pharmacol 2006;97-112

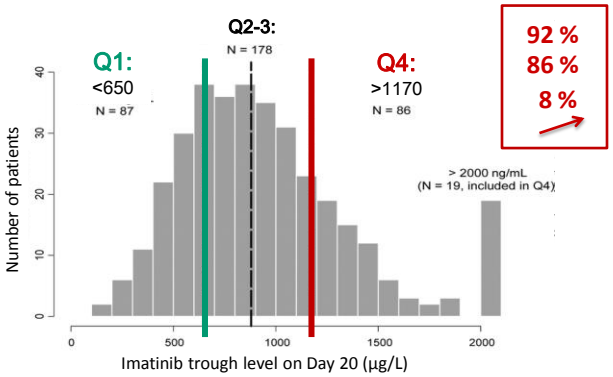
Importance clinique de la PK

Sous-analyse de l'étude IRIS : PK de l'imatinib et corrélation avec la réponse et la tolérance dans la LMC

Outcome :

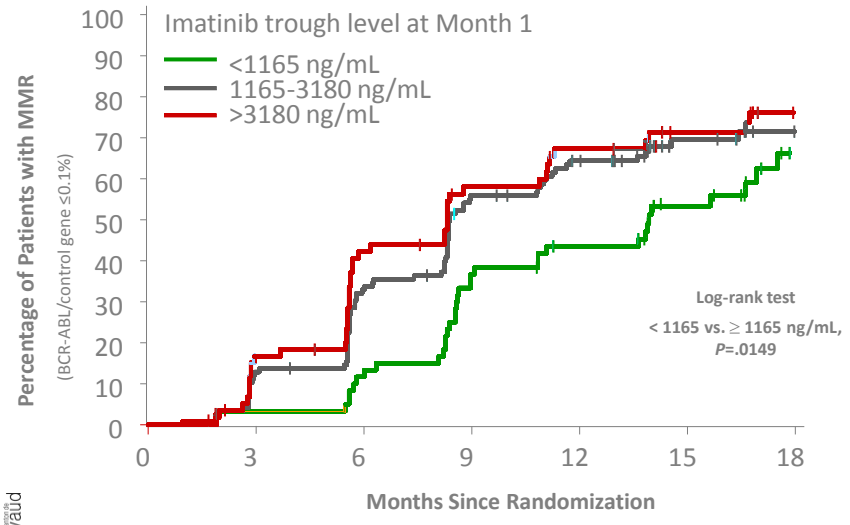
CCyR 5 yr	76 %
MMR 2 yr	63 %
Escape	18 % ↘
ADR	

Concentration résiduelle (C_{min}) :



Larson et al. Imatinib pharmacokinetics and its correlation with response and safety … Blood 2008;111(8):4022-4028

Corrélation entre C_{min} à 1 mois et délai de réponse moléculaire majeure

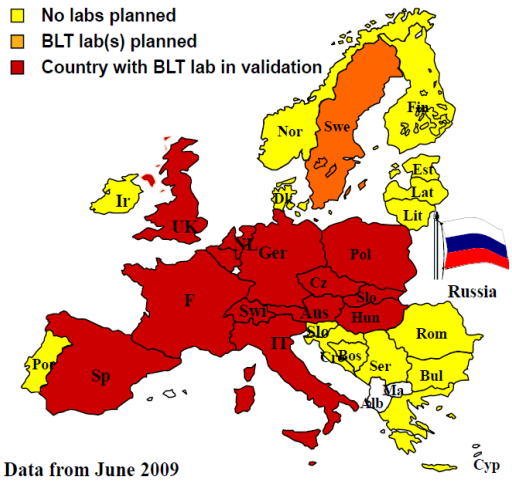


Un fabricant en faveur du TDM ?

NOVARTIS ONCOLOGY

EUTOS for CML
European Treatment and Outcome Study

ELN European LeukemiaNet



FDA U.S. Food and Drug Administration

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Novartis Oncology 4/21/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

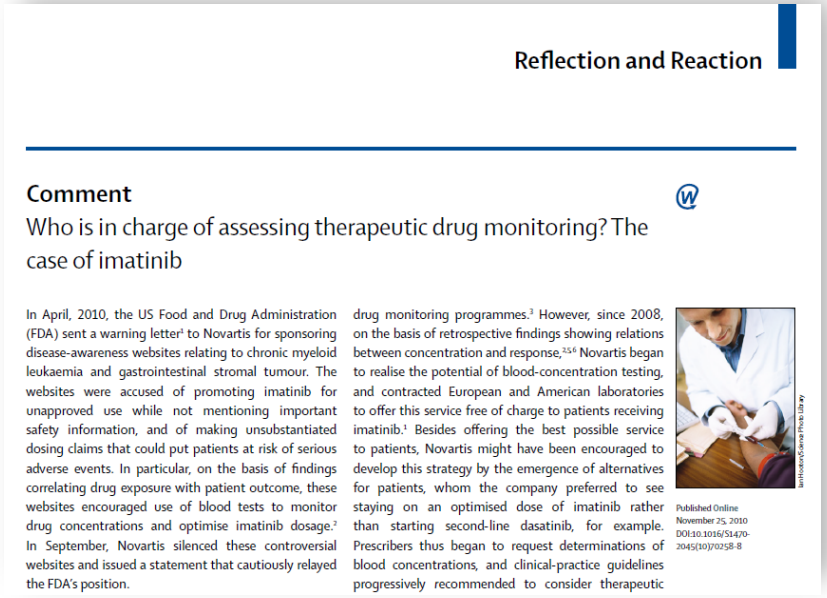
Ludwig Hantson, Ph.D.
CEO
Novartis Pharmaceuticals Corporation
One Health Plaza

WARNING LETTER

Dear Dr. Hantson:

As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed two websites (www.gistalliance.com and www.cmlalliance.com) sponsored by Novartis. As explained more fully below, these websites represent branded promotional material for Gleevec® (imatinib mesylate) (Gleevec). These websites are false and misleading because they promote the drug for an unapproved use, fail to disclose the risks associated with the use of Gleevec and make unsubstantiated dosing claims. [1] Therefore, these websites misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a), (f)(1) & (n); 321(n), and FDA implementing regulations. *See* 21 CFR 201.100(c), 201.115 & 201.128, 21 CFR 202.1(e)(5), (e)(6)(i), (iv) & (xi). Furthermore, it appears that these materials were neither submitted to FDA 30 days prior to the intended time of initial dissemination or initial publication as required by 21 CFR

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm210191.htm



Reflection and Reaction

Comment

Who is in charge of assessing therapeutic drug monitoring? The case of imatinib

In April, 2010, the US Food and Drug Administration (FDA) sent a warning letter[1] to Novartis for sponsoring disease-awareness websites relating to chronic myeloid leukaemia and gastrointestinal stromal tumour. The websites were accused of promoting imatinib for unapproved use while not mentioning important safety information, and of making unsubstantiated dosing claims that could put patients at risk of serious adverse events. In particular, on the basis of findings correlating drug exposure with patient outcome, these websites encouraged use of blood tests to monitor drug concentrations and optimise imatinib dosage.[2] In September, Novartis silenced these controversial websites and issued a statement that cautiously relayed the FDA's position.

drug monitoring programmes.[3] However, since 2008, on the basis of retrospective findings showing relations between concentration and response,[2,5,6] Novartis began to realise the potential of blood-concentration testing, and contracted European and American laboratories to offer this service free of charge to patients receiving imatinib.[1] Besides offering the best possible service to patients, Novartis might have been encouraged to develop this strategy by the emergence of alternatives for patients, whom the company preferred to see staying on an optimised dose of imatinib rather than starting second-line dasatinib, for example. Prescribers thus began to request determinations of blood concentrations, and clinical-practice guidelines progressively recommended to consider therapeutic

Published Online
November 25, 2010
DOI:10.1016/S1470-2045(10)70258-8

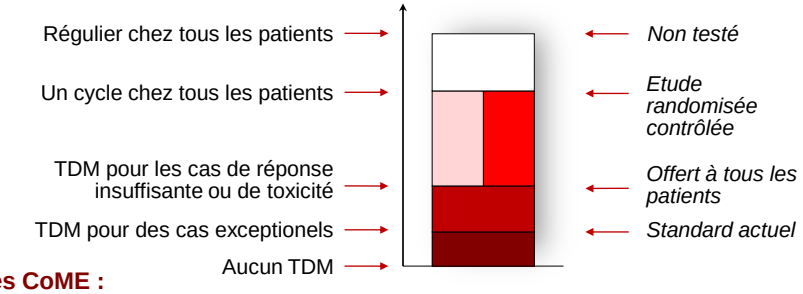
Buclin T, Widmer N, Biollaz J, Decosterd LA. Lancet Oncol. 2011;12:9-11.

CoME : Concentration Monitoring Evaluation : la voie vers un *Evidence-Based TDM*

Considérations:

- Les programmes de TDM reposent le plus souvent sur un développement empirique
- Dès qu'une mesure est disponible, il devient extrêmement difficile de comparer *TDM* versus *pas de TDM* (études peu acceptables)

Question de substitution : *Combien de TDM ?*



Etudes CoME :

- Chez des patients recevant le médicament (stratifiés selon durée de traitement)
- Comparaison entre *TDM routine* versus *TDM rescue* (i.e. en cas de problème clinique)
- Issue composite : problème clinique (efficacité insuffisante ou toxicité)

Le Projet ISyPeM I (2010-2013)

Carlotta Guiducci, Thierry Buclin, Giovanni De Micheli, Christian Enz, Carlos-A Pena-Reyes

Intelligent Systems for Personalized Medicine

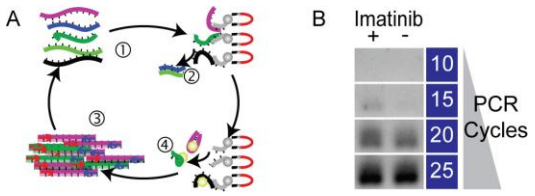
Buts :

Avancer en direction d'une médecine personnalisée en proposant de nouvelles technologies pour le monitoring des concentrations de médicaments et le contrôle de leur administration qui combinent localement la mesure, le traitement des données et les instructions posologiques.

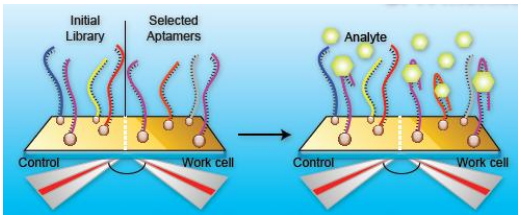
→ **Principes de base pour ISyPeM II**

WP1: Sensor Technology

Aptamers:



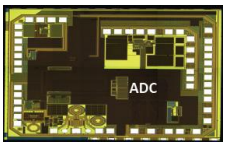
Lab on Chip:

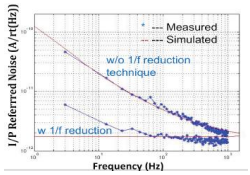


Rôles du CHUV : Identification des candidats au TDM, fourniture d'échantillons cliniques, mesure de concentrations par les méthodes de référence (ex. tobramycin FPIA vs LCMS)

WP2: Chip Architecture and Operation

Asynchronous Biomedical Sensor Interface:





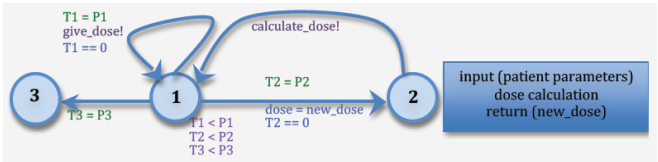
Embedded software:

Chip software
Radio communication
Power management
User/network interfaces

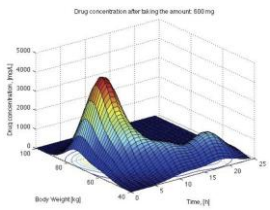
Rôles du CHUV : Insisté sur l'importance d'une assistance à l'interprétation des résultats de mesure en termes d'adaptation posologique → projet EzeCHieL *add-on*

WP3: Process Validation

Modelling and Verification:



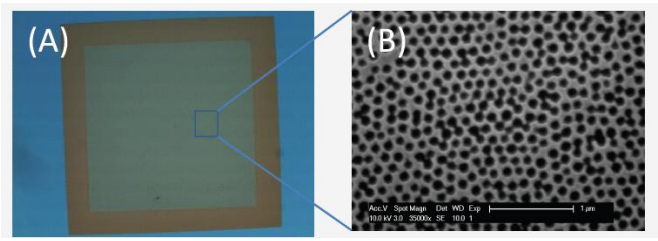
Alternative algorithms for TDM:



Rôles du CHUV : Description des procédures actuelles du TDM

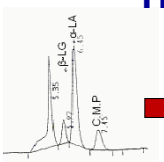
WP4: Controlled Delivery

Controllable permeability nanomembranes:

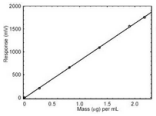


Rôles du CHUV : (insignifiant)

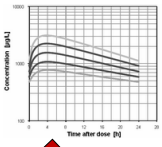
TDM: l'approche traditionnelle



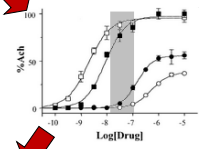
Qu'est-ce que j'observe ?
Signal chimique



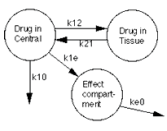
Quelle est ma position ?
Concentration



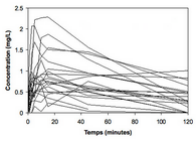
Où cela me situe-t-il ?
Percentiles



Est-ce là que je dois être ?
Cible thérapeutique



Où devrais-je aller ?
Prédiction pharmacocinétique



Laisser une trace ?
Archivage

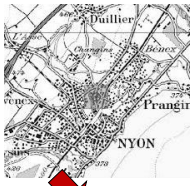
Comment y aller ?
Ajustement posologique

Buclin T, Gotta V, Fuchs A, Widmer N, Aronson J. Monitoring drug therapy. Br J Clin Pharmacol. 2012;73:917-23

Trouver son chemin: l'approche traditionnelle

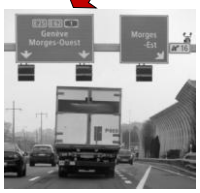
Qu'est-ce que j'observe ?
Soleil, étoiles, pole Nord

Quelle est ma position ?
Coordonnées

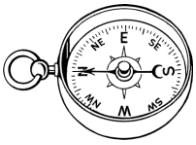


Où cela me situe-t-il ?
Carte

Est-ce là que je dois être ?
Addresse



Où devrais-je aller ?
Panneaux indicateurs



Comment y aller ?
Boussole

Laisser une trace ?
Carte postale, SMS

Trouver son chemin au XXI^{eme} siècle

Qu'est-ce que j'observe ? Signal GPS

Quelle est ma position ? Calcul de coordonnées

Où cela me situe-t-il? Carte intégrée

Est-ce là que je dois être ? Adresse introduite

Où devrais-je aller ? Calcul du chemin

Comment y aller ? Instructions

Laisser une trace ? Points transmis par GSM

Drug Monitoring, XXIst Century

Qu'est-ce que j'observe ? Transduction chimique

Quelle est ma position ? Concentration déduite

Où cela me situe-t-il? Percentiles intégrés

Est-ce là que je dois être ? Cible thérapeutique

Où devrais-je aller ? Prédiction PK

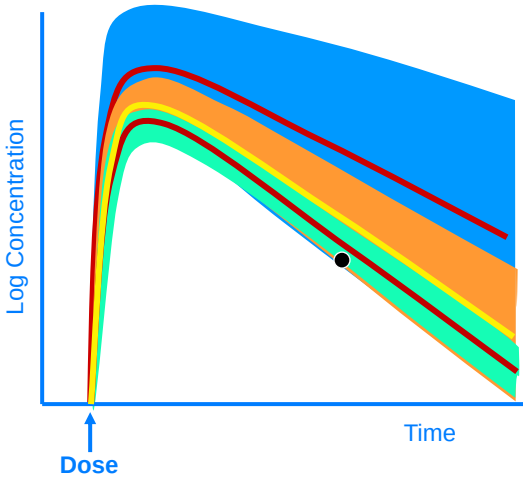
Comment y aller ? Ajustement posologique

Laisser une trace ? Archivage via GSM

Pharmacokinétique de Population

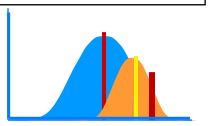
$C_{ij} = f(D,t, CL_i, V_i, F_i, k_a) + \varepsilon_{ij}$

e.g. $CL_i = g(z, CL_{pop}) + \eta_i$



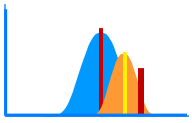
Paramètres moyens

variabilté inter-sujets



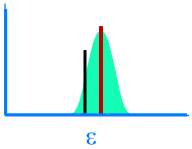
Moyenne de groupe

variabilité inexpliquée

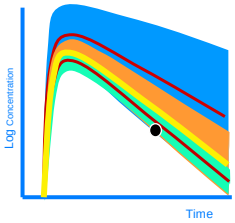


Individuelle

variabilté intra-sujet



Adaptation Bayésienne



Vraisemblance de la valeur du paramètre H_i pour le sujet *i* :

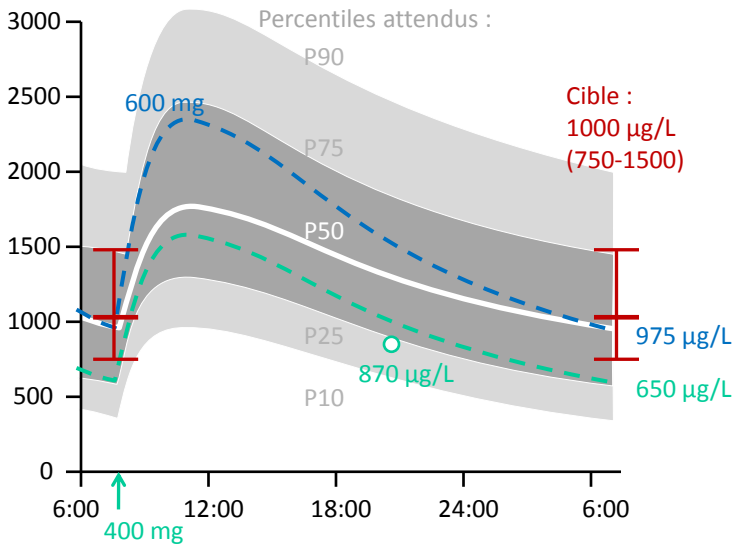
$$P(H_i \mid C_{obs}) = \frac{P(C_{obs} \mid H_i) \cdot P(H_i)}{P(C_{obs})}$$

Trouver H_i qui minimise la somme des carrés pondérée (~ - 2 Log-Likelihood) :

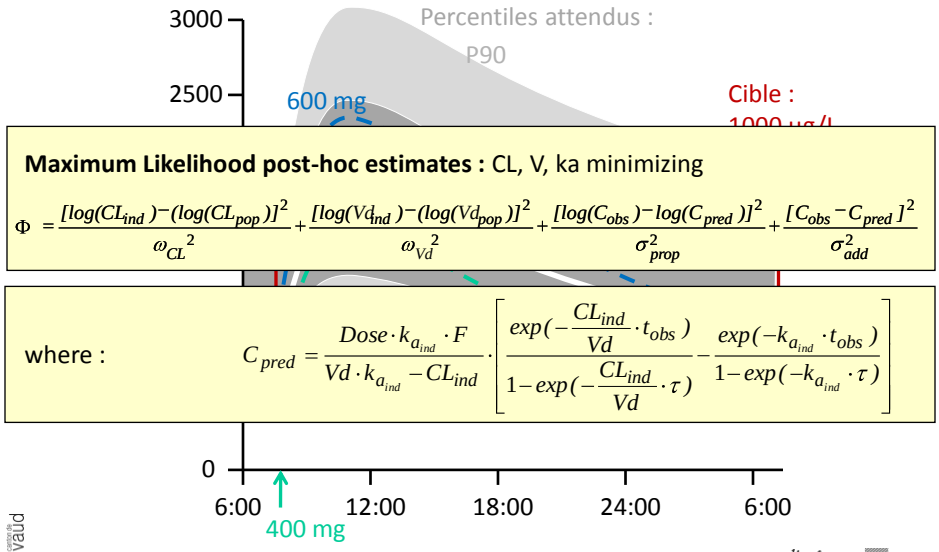
$$\Phi = \sum \frac{(C_{obs} - C_{pred})^2}{\sigma_\varepsilon^2} + \frac{(CL_i - CL_{pop})^2}{\sigma_{CL}^2} + \frac{(V_i - V_{pop})^2}{\sigma_V^2} + \text{etc.}$$

Où C_{pred} est donnée par les équations PK utilisant CL_i, V_i …

Ajustement posologique Bayésien



Ajustement posologique Bayésien



Maximum Likelihood post-hoc estimates : CL, V, ka minimizing

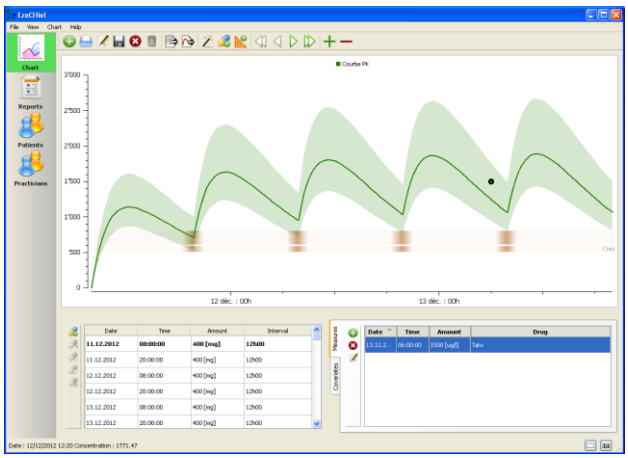
$$\Phi = \frac{[log(CL_{ind}) - (log(CL_{pop})]^2}{\omega_{CL}^2} + \frac{[log(Vd_{ind}) - (log(Vd_{pop})]^2}{\omega_{Vd}^2} + \frac{[log(C_{obs}) - log(C_{pred})]^2}{\sigma_{prop}^2} + \frac{[C_{obs} - C_{pred}]^2}{\sigma_{add}^2}$$

where :

$$C_{pred} = \frac{Dose \cdot k_{a_{ind}} \cdot F}{Vd \cdot k_{a_{ind}} - CL_{ind}} \cdot \left[\frac{exp(-\frac{CL_{ind}}{Vd} \cdot t_{obs})}{1 - exp(-\frac{CL_{ind}}{Vd} \cdot \tau)} - \frac{exp(-k_{a_{ind}} \cdot t_{obs})}{1 - exp(-k_{a_{ind}} \cdot \tau)} \right]$$

Add-On: projet EzeCHieL

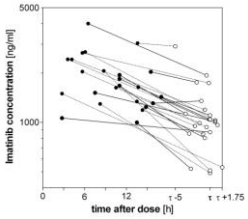
A user-friendly tool for computer-assisted interpretation of TDM results



Clinical Validation of the Algorithm

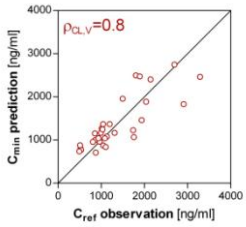
Prediction of imatinib C_{min} using Bayesian MAP

Observed ● C_{random} & ○ C_{min}



Use ● C_{random} & PK model
⇨ predict C_{min} ○

comparison:
Observed C_{min} *versus* predicted C_{min}



ORIGINAL RESEARCH ARTICLE

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Therapeutic Drug Monitoring of Imatinib

Bayesian and Alternative Methods to Predict Trough Levels

Verena Gotta,[1,2] Nicolas Widmer,[1] Michael Montemurro,[3] Serge Leyvraz,[3] Amina Haouala,[1] Laurent A. Decosterd,[1] Chantal Csajka[1,2] and *Thierry Buclin[1]*

Clin Pharmacokinet
DOI 10.1007/s40262-012-0020-y

REVIEW ARTICLE

Benchmarking Therapeutic Drug Monitoring Software: A Review of Available Computer Tools

Aline Fuchs · Chantal Csajka · Yann Thoma · Thierry Buclin · Nicolas Widmer

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Abstract Therapeutic drug monitoring (TDM) aims to optimize treatments by individualizing dosage regimens based on the measurement of blood concentrations. Dosage individualization to maintain concentrations within a target range requires pharmacokinetic and clinical capabilities. Bayesian calculations currently represent the gold standard TDM approach but require computation assistance. In recent decades computer programs have been developed to assist clinicians in this assignment. The aim of this survey was to assess and compare computer tools designed to support TDM clinical activities. The literature and the Internet were searched to identify software. All programs were tested on personal computers. Each program was scored against a standardized grid covering pharmacokinetic relevance, user friendliness, computing aspects, interfacing and storage. A weighting factor was applied to representative clinical vignettes were processed through each of them. Altogether, 12 software tools were identified, tested and ranked, representing a comprehensive review of the available software. Numbers of drugs handled by the software vary widely (from two to 180), and eight programs offer users the possibility of adding new drug models based on population pharmacokinetic analyses. Bayesian computation to predict dosage adaptation from blood concentration (a posteriori adjustment) is performed by ten tools, while nine are also able to propose a priori dosage regimens, based only on individual patient covariates such as age, sex and bodyweight. Among those applying Bayesian calculation, MM-USC*PACK© uses the non-parametric approach. The top two programs emerging from this benchmark were MwPharm© and TCIWorks. Most other programs evaluated had good

Le Projet ISyPeM II (2013-2016)

Carlotta Guiducci, Thierry Buclin, Christian Heinis, Philippe Renaud, Michael Ignaz Schumacher, Jean-Manuel Segura, Martial Geiser, Marc Pfeifer, Yann Thoma

Therapeutic Drug Monitoring for Personalized Medicine

But:

Développer un système intégré *point-of-care* capable de:

(i) Mesurer des concentrations de médicament dans le sang via un système compact intégré;

(ii) Informer le prescripteur sur l'exposition du patient par rapport à la population de référence et suggérer un ajustement posologique;

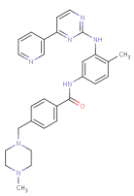
(iii) Collecter des données d'utilisation dans une base centrale en vue de raffiner les procédures d'ajustement posologique

Démonstrateurs

Nouveaux anticancéreux

IMATINIB

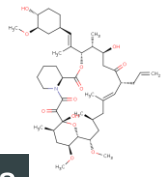
1000 ng/ml
493.60 Da



Immunosuppresseurs

TACROLIMUS

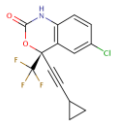
10 ng/ml
804.02 Da



Antiretroviraux

EFAVIRENZ

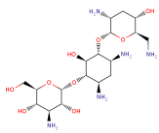
2000 ng/ml
315.70 Da



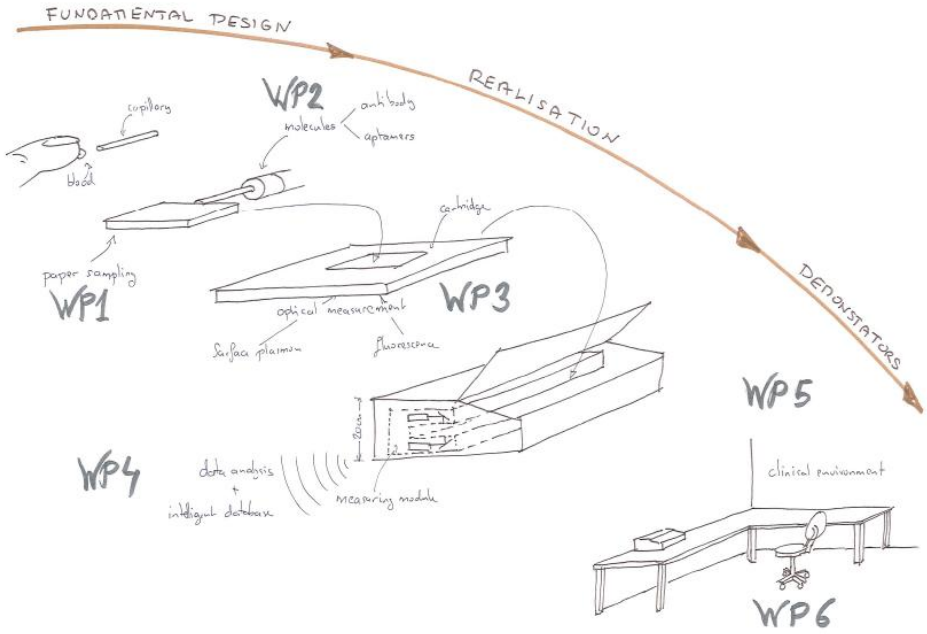
Antibiotiques

TOBRAMYCINE

1000 ng/ml
467.5 Da

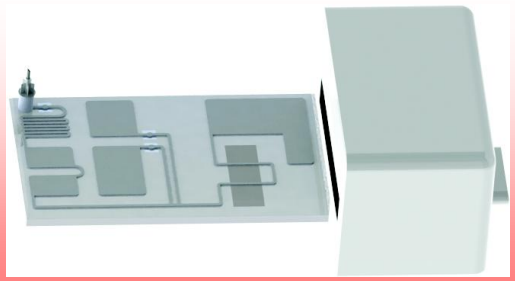


Pharmacologie et Toxicologie cliniques



WP1: Sample Preparation

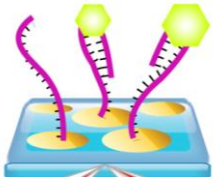
Microfluidics, derivatization etc.:



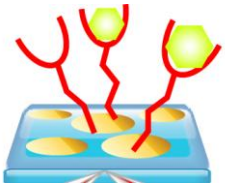
Rôles du CHUV : Fournir des échantillons cliniques et une expertise sur les aspects pré-analytiques et analytiques

WP2: Selective Capturing Molecules

Aptamers :



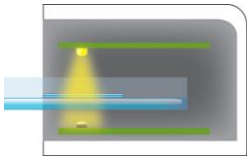
Antibodies:



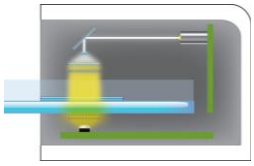
Rôles du CHUV : Mesurer les concentrations par des méthodes de référence; contribuer à résoudre les aspects analytiques

WP3: Miniaturized Drug Detection

Surface Plasmon Resonance:

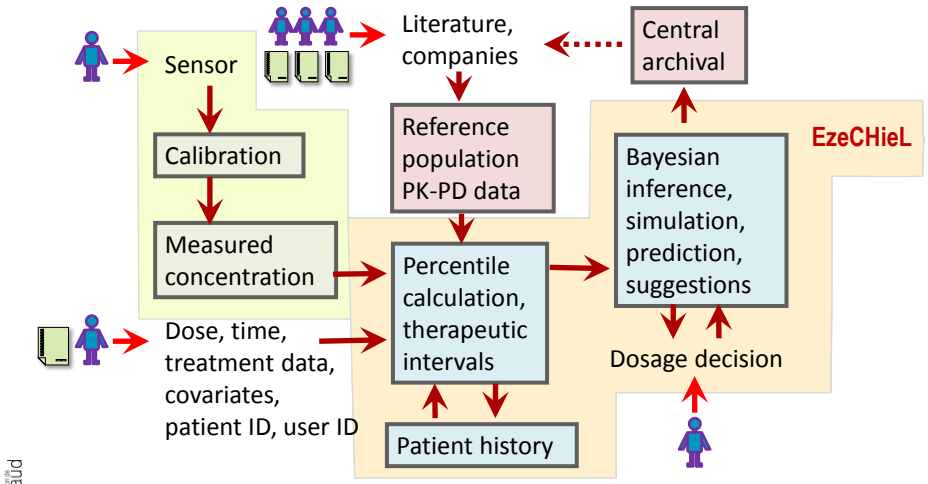


Fluorescence Polarization:

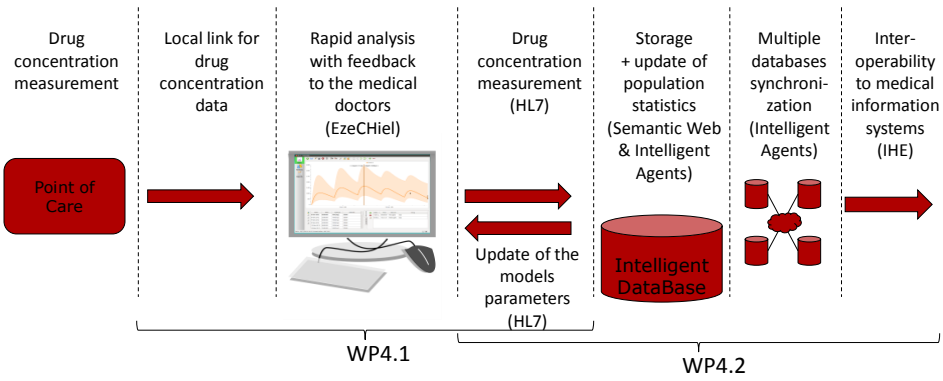


Rôles du CHUV : Mesurer les concentrations par des méthodes de référence; contribuer à résoudre les aspects analytiques

WP4: Data Analysis, Interoperability and Intelligent Databases



WP4: Data Analysis, Interoperability and Intelligent Databases



Rôles du CHUV : **Diriger le développement algorithmique et ergonomique d'EzeCHieL**

Politique

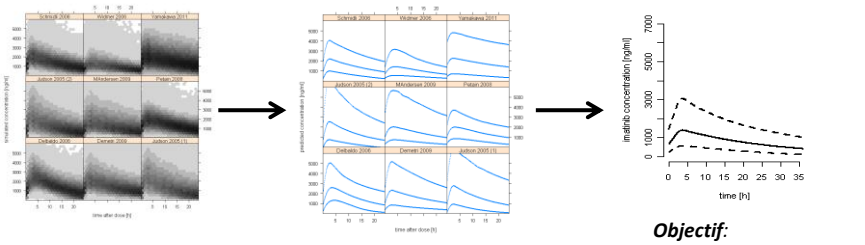
- Développement rapide des aspects logiciels
- Architecture modulaire, interoperabilité, evolutivité
- Recours aux standards classiques (XML HL7…)
- Diffusion libre en *open source*
- Compilation multi-plateformes (PC, Mac, Palm…)
- Ergonomie et *user friendliness* (professionels & patients)
- Implémentation au TDM du laboratoire (connectivité avec les systèmes de laboratoire)
- Compilation des données de référence
- Dissemination large parmi les professionels
- Réseau collaboratif d'utilisateurs
- Intégratation finale à l'appareil de mesure *point of care*

WP5: Demonstrator Prototype

Rôles du CHUV : **Validatation de l'utilisation clinique par comparaison au TDM traditionnel; planification d'essais cliniques**

WP6: Reference PKPD Data

Systematic population PKPD reviews : méta-analyse de modèles publiés



Simulation de données selon 9 modèles publiés

9 courbes de percentiles ☹

Objectif:
1 méta-modèle résumant les paramètres de référence pour le TDM☺

Rôles du CHUV : **Supervision des approches biostatistiques** (collaboration IUMSP); **Test et utilisation de l'outil R une fois développé**

REVIEW ARTICLE

Systematic Review of Population Pharmacokinetic Analyses of Imatinib and Relationships With Treatment Outcomes

Verena Gotta, PharmD,† Thierry Buclin, MD,* Chantal Csajka, PhD,*† and Nicolas Widmer, PhD**

Abstract: Several population pharmacokinetic (PPK) analyses of the anticancer drug imatinib have been performed to investigate different patient populations and covariate effects. The present analysis offers a systematic qualitative and quantitative summary and comparison of those. Its primary objective was to provide useful information for evaluating the *expectedness* of imatinib plasma concentration measurements in the frame of therapeutic drug monitoring. The secondary objective was to review clinically important concentration-effect relationships to provide help in evaluating the potential *suitability* of plasma concentration values. Nine PPK models describing total imatinib plasma concentration were identified. Parameter estimates were standardized to common covariate values whenever possible. Predicted median exposure (C_{min}) was derived by simulations and ranged between models from 555 to 1388 ng/mL (grand median: 870 ng/mL and interquartile "reference" range: 520–1390 ng/mL). Covariates of potential clinical importance (up to 30% change in pharmacokinetic predicted by at least 1 model) included body weight, albumin, α_1 acid glycoprotein, and white blood cell patient characteristics. For future research, external PPK model validation or meta-model development should be considered.

Key Words: tyrosine kinase inhibitors, drug monitoring, oncology, simulation, meta-analysis

(*Ther Drug Monit* 2013;35:150–167)

INTRODUCTION

Therapeutic drug monitoring (TDM) of the targeted anticancer drug imatinib (Glivec, Gleevec; Novartis Pharma, Basel, Switzerland) has been suggested as decision support for potential dosage adaptation at least in selected cases of chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST) with clinical concerns.[1–9] Prescribers thus increasingly come across plasma concentration measurements and have to interpret them. Two main questions should be addressed by the clinician when facing imatinib TDM values.

Gotta V, Buclin T, Csajka C, Widmer N. Systematic review of population pharmacokinetic analyses of imatinib and relationships with treatment outcomes. Ther Drug Monit. 2013;35(2):150-67

Conclusion

- Le TDM mérite probablement d'être étendu à nombre de médicaments critiques à PK variable administrés au long cours (immunosuppresseurs, antiviraux, antifongiques, anticancéreux ciblés etc.)
- Cela va nécessiter des systèmes *point-of-care* capables de mesurer des concentrations et de délivrer en ligne des interprétations et des recommandations d'ajustement posologique
- Une culture globale du monitoring se développe et affectera les prescripteurs, les pharmaciens, les firmes pharmaceutiques, les autorités, les professionnels de la santé et les patients (concentrations, biomarqueurs d'effet, de toxicité)
- Le cadre conceptuel du monitoring devra se préciser, et des confirmation fondées sur de bonnes preuves devront être obtenues