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The impact of gastric acid suppressive agents on pazopanib exposure

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Background
Pazopanib has been registered for advanced soft tissue sarcoma (STS) and metastatic renal cell carcinoma (mRCC). The uptake of pazopanib is 40% reduced when a proton pump inhibitor is concomitantly used. Nevertheless, still a large group of cancer patients need a form of gastric acid suppressive agents (GAS, e.g. proton pump inhibitors or H2-anagonists) due to gastrointestinal adverse events. Recently, it was demonstrated that the use of pazopanib with GAS resulted in shorter overall survival and progression free survival in patients with STS. In order to limit the effect of GAS on pazopanib absorption, the advice is to take the GAS 1 hour after pazopanib. In that way the pazopanib is dosed at the lowest gastric pH value. However, the effect of this most optimal controlled intake on pazopanib absorption is unknown. Therefore, we investigated whether this controlled intake algorithm affects pazopanib exposure.

Methods
In the DIET study, pazopanib trough concentrations (Ctrough) were measured at predefined moments. In this study a total of 80 patients with mRCC and STS were included. The concomitant use of GAS was recorded and taken according the intake algorithm. Patients were subdivided into two groups (with GAS or without GAS).

Results
Of the 80 patients, 22 patients were treated with pazopanib in combination with GAS. In patients treated with pazopanib without GAS the geometric mean(GM) pazopanib Ctrough level was 29.1 mg/L (95% CI 26.4 -31.8) compared to 22.4 mg/L (95% CI 18.0-27.8) (p = 0.01) in those treated with GAS.

Conclusion: Patient who use pazopanib with controlled intake of GAS had a 23% lower pazopanib exposure. Therefore, we advice that in patients, who are unable to quit their GAS agent, pazopanib trough concentrations should be monitored in order to prevent shorter treatment benefit.

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Performance Characteristics of a Modified HIV-1 Drug Resistance Genotyping Method for use in Resource Limited Settings

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Background: HIV-1 drug resistance (HIVDR) assays are critical components of HIV clinical management programs in the face of emerging drug resistance. However, the high costs associated with existing commercial HIVDR assays prohibit their routine usage in resource-limited settings. We present the performance characteristics of a modified commercial HIVDR testing assay.
Methods: A total of 26 plasma samples were used to validate and assess the accuracy, precision, reproducibility and amplification sensitivity of a modified HIVDR assay by HIV genotyping. In addition, a cost comparison between the original and the modified assay was performed using the ingredient costing approach.
Results: The performance characteristics of the modified assay were in agreement with the original assay. Accuracy, precision and reproducibility showed nucleotide sequence identity of 98.5% (confidence interval (CI), 97.9–99.1%), 98.67% (CI, 98.1–99.23) and 98.7% (CI, 98.1–99.3), respectively. There was no difference in the type of mutations detected by the two assays ($\chi 2 = 2.36$, $p = 0.26$). Precision and reproducibility showed significant mutation agreement between replicates (kappa = 0.79 and 0.78), respectively ($p < 0.05$). The amplification sensitivity of the modified assay was 100% and 62.5% for viremia ≥1000 copies/ml and <1000 copies/ml respectively. Our assay modification translates to a 39.2% reduction in the cost of reagents.
Conclusion: Our findings underscore the potential of modifying commercially available HIVDR testing assays into cost-effective, yet accurate assays for use in resource-limited settings.

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Epigenetic Regulation of OCTN1-mediated Cytarabine Transport in Acute Myeloid Leukemia

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Background:
Cytarabine is used as first-line therapy in acute myeloid leukemia (AML) and is reported to be transported into leukemic cells via OCTN1. One hallmark of AML is dysregulation at the genetic and epigenetic level. Currently, clinical trials are underway using methyltransferase inhibitors such as 5-azacytidine or decitabine to "epigenetically prime" AML patients and reverse these epigenetic dysregulations (NCT03164057). These clinical trials would benefit from a stronger understanding of the mechanism underlying improved patient outcomes. Here, we tested our hypothesis that these improved patient outcomes are due to epigenetic modifications impacting OCTN1 expression, intracellular accumulation of cytarabine and subsequent antileukemic effects in AML cells.

Materials and Methods:
Uptake and cytotoxicity studies were performed in AML cell lines with prior 3-day treatment with hypomethylating agent, decitabine. Uptake was conducted by using radioactive substrates and quantified by scintillation counts. OCTN1 expression levels were compared between treated and untreated AML cells with normalization to GAPDH. Methylation profiles were determined using bisulfite modification and pyrosequencing (BS-Seq). Cytarabine cytotoxicity was determined via MTT and developed after 72 hours of treatment. A Student's t-test was used to determine group differences, and $P < 0.05$ was considered a cutoff for statistical significance.

Results:
Cytarabine uptake (1 µM; 15 min) and cytotoxicity (72 hours) varied among the 10 AML cell lines studied and were used to categorize "high" and "low" uptake. AML cell lines that showed low uptake had consistently higher methylation patterns in CpG islands upstream of SLC22A4 (OCTN1) as determined by BS-Seq. Exposure to 500 nM of hypomethylating agent decitabine for 72 hours increased OCTN1 expression (5.0 fold), uptake of cytarabine (2.9 fold), and subsequent cytotoxicity (6.2 fold) in CHRF-288-11 cells with low basal OCTN1 expression. In contrast, lower methylated cell line OCI-AML3 showed modest to no significant increases in OCTN1 (1.2 fold), uptake of cytarabine (1.5 fold) and cytotoxicity (3.3 fold) following decitabine treatment. These findings are consistent with the notion that methylation of OCTN1 was inversely related to cytarabine uptake.

Conclusions:
These results identify SLC22A4 (OCTN1) methylation status as a contributor to the expression of OCTN1, cellular uptake, and efficacy of cytarabine; these results have broad implications for the future design of combination chemotherapy regimens.

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Pharmacokinetics of Mitomycin-c Lipidic Prodrug Entrapped in Liposomes (Promitil) and Clinical Correlations in Metastatic Colorectal Cancer Patients

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Background: Pegylated liposomal mitomycin-c lipidic prodrug (Promitil) may be useful agent in patients with advanced (3rd line) colo-rectal carcinoma (CRC). We report here on the pharmacokinetics and clinical correlations within a phase 1A/B study.
Methods: In 53/72 CRC patients, who received Promitil either as single agent or in combination with capecitabine and/or bevacizumab, plasma levels of mitomycin-c lipidic prodrug (MLP) were determined. Plasma levels of the liposomal active ingredient, mitomycin-c lipidic prodrug (MLP), were determined by an HPLC UV assay, and the pharmacokinetics of MLP was analyzed by noncompartmental methods. Unpaired t tests, linear regression analysis and Pearson or Spearman correlation coefficients were used for statistical analysis.
Results: Promitil was well tolerated with a safety profile similar as previously reported. Stable Disease was reported in 15/36 (42%) of efficacy-evaluable patients. Median survival of stable disease patients (14.4 months) was significantly longer than of progressive disease patients (6.5 months) and non-evaluable patients (2.3 months). MLP pharmacokinetics was stealth-like with long T½ (~1 day), slow clearance, and small volume of distribution (Vd). The addition of capecitabine and/or bevacizumab did not have any apparent effect on the pharmacokinetics of MLP, safety, and clinical outcome. A high baseline neutrophil count and high baseline CEA were correlated with faster clearance, and larger Vd. Stable disease patients had longer T½ and slower clearance than other patients. T½ and clearance were significantly correlated with survival.
Conclusions: Promitil treatment results in a substantial rate of disease stabilization in pre-treated, chemo-refractory, metastatic CRC, and in prolonged survival in patients achieving stable disease. The correlation of neutrophil count and CEA level with critical pharmacokinetic parameters of the liposomal prodrug is a novel finding and needs to be further investigated. Importantly, the association of long circulation time of liposomal MLP with stable disease and longer survival is consistent with an improved probability of disease control resulting from enhanced tumor localization of long-circulating liposomes and underscores the relevance of personalized pharmacokinetic evaluation in the clinical use of nanomedicines.

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Investigation of Age-Dependency in Ewing Sarcoma Induction Therapy Using a Population Pharmacokinetic Modelling Approach

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Background: Ewing sarcoma is a very aggressive bone tumour, which often occurs in adolescents or young adulthood. The incidence of treatment-associated toxicity varies significantly between children, adolescents and adults. These toxicities are often worse in young children and reduce with advancing age. Furthermore, survival rates differ between age groups, with younger patients generally having a better outcome as compared to older patients. The standard induction therapy of Ewing sarcoma patients includes the drugs vincristine (V), ifosfamide (I), doxorubicin (D), etoposide (E) and cyclophosphamide (C). Population pharmacokinetic (popPK) modelling of these drugs can help to further elucidate age-dependent differences in toxicity and survival of Ewing sarcoma patients and therefore potentially improve therapy.

Material & Methods: The Northern Institute for Cancer Research (NICR) at Newcastle University is conducting a clinical pharmacology study to investigate differences in drug disposition between Ewing sarcoma patients of different ages and early drug toxicity in this patient population (short title: PK 2013 01; EUDRACT Number: 2013-000052-17). In total, 120 Ewing sarcoma patients treated with standard dose induction chemotherapy (VIDE or VDC/IE), will be recruited to the study. Blood samples are collected from patients at defined time points for quantification of plasma drug concentrations on a single course of VIDE or VDC/IE treatment. So far, data obtained from over 70 patients are available for these drugs for the development of popPK models using NONMEM®.

Results: Appropriate popPK models have been developed and the effects of covariates including age and gender on the PK parameters have been analysed. Based on the preliminary analysis, there are no differences in the PK of vincristine, ifosfamide, doxorubicin and etoposide with age or gender. Furthermore, the PK parameters of the different drugs are tested for potential correlations between drugs. In this patient population the vincristine clearance seems to correlate significantly with doxorubicin clearance ($r=0.407$, $p=0.009$).

Conclusions: Preliminary data suggest that there are no differences in the PK of vincristine, ifosfamide, doxorubicin and etoposide with age or gender. Once data are available for all patients the models will be revised and both the covariate analysis and the potential relations between PK parameters of the different drugs will be renewed. These analyses could help to further elucidate the differences in toxicity and survival of Ewing sarcoma patients and therefore potentially serve to develop strategies to improve future therapy.

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Quantitative modeling of inter-lesion and inter-organ variability of tumor size

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Background: In metastatic cancer, the growth and drug-induced shrinkage of individual tumor lesions may be highly dependent on the microenvironment of the hosting organ, and individual lesions may contribute differently to overall disease progression and survival. In the traditional tumor response analysis, the sum of longest diameters (SLD) is considered and impact of individual lesion dynamics on the outcome is ignored. The objectives of this analysis were

- to develop population models to characterize the differences in tumor dynamics between lesions and between metastatic sites, dropout from lesion measurements, and the appearance of new lesions
- investigate the predictability of lesion dynamics and new lesion appearance on overall survival (OS)

Methods: The dataset consisted of lesion measurement data (up to 10 lesions) from 183 subjects with metastatic HER2-negative breast cancer receiving docetaxel at the dose of 100 mg/m2 on the first day of three-week treatment cycles. A tumor growth inhibition model that characterizes both lesion growth and drug-induced lesion shrinkage. Inter-lesion (ILV), inter-organ (IORV), and inter-individual variability (IIV) were explored in lesion baseline, growth rate and drug-induced tumor shrinkage parameters. Logistic regression models were developed to describe the observed dropout from lesion measurements and the appearance of new lesions. The observed survival data were described using a parametric time-to-event model with Weibull distribution.

Results: Out of 7 different metastatic sites, liver (50%), lymph nodes (46%) and lungs (26%) were the most frequent locations. The median number of lesions per subject was 3 and 44% of the population had more than one metastatic site. Lesions showed diverse profiles of shrinkage and growth during the study, but were more similar within an organ than between organs.

The lesion model included a typical baseline value for each organ, along with IIV (28 %CV), and ILV that ranged from similar magnitude (soft tissue) and up to two times higher (breast) compared to the IIV. The growth rate constant was associated with very high IIV (135%CV) and IORV (172 %CV). The drug-induced shrinkage rate was almost twice as high for liver compared to the other organs and the IIV and IORV of similar magnitude (50 %CV).

The probability to dropout from tumor size measurements increased with the appearance of a new lesion, 20% increase from SLD nadir, and time. The predictors of new lesion were size of largest target lesion, presence of more than 2 liver lesions, and treatment duration. The hazard of death increased with appearance of new lesion and increase in SLD.

Conclusion: Inter-lesion, inter-organ, and inter-individual differences were well captured by the developed lesion model. This modeling approach, separating different levels of variability, has the potential to provide a better understanding of drug effect in different organs, and may be used to tailor treatments based on lesion location, lesion size and early lesion response. The preliminary results from survival analysis shows that appearance of a new lesion, along with tumor size time-course are significant predictors of OS. In a next step, the individual lesion dynamics will be explored as predictors of survival.

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Influence of genetic variation in COMT on cisplatin-induced nephrotoxicity in cancer patients.

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Background

Cisplatin is a widely used chemotherapeutic agent for multiple indications. Unfortunately, in a substantial set of patients treated with cisplatin acute kidney injury (AKI) occurs. A recent case report suggested single nucleotide polymorphisms (SNPs) in the COMT gene might be associated with increased cisplatin-induced nephrotoxicity (de Jong et al., BJCP, 2017). Here, we assessed the association of 3 SNPs in this gene with cisplatin-induced nephrotoxicity in our patient population.

Methods

Whole blood samples and serum creatinine concentrations (Scr) of patients who received cisplatin between 2004-2019 in the Erasmus MC and who had provided informed consent to perform DNA genotyping were included in this analysis. (Erasmus MC study number MEC 02.1002)

The 1947 G>A (Val158Met, rs4680), c.615 + 310 C>T (rs4646316) and c.616 – 367 C>T (rs9332377) SNPs were associated with AKI grade 3 (CTCAE v4.03) using Fisher's exact test up to 2 weeks prior to and up to 6 weeks after cisplatin treatment was described.

Results

A total of 551 patients were included in this study. Median Scr at baseline was 70 µmol/l (inter quartile range (IQR) 59-81). Up to six weeks after the start of cisplatin treatment the median increased to 81 µmol/l (IQR 69-96).

The presence of a variant of COMT c.616-367C>T was significantly associated with a decreased incidence of AKI grade 3 when performing a recessive analysis (CC vs CT + TT; OR: 0.201; 95%CI: 0.047-0.861; p=0.014). AKI grade 3 was also significantly associated with age ≥65 years (OR:2.464; 95%CI: 1.095-5.542; p=0.025). Due to the low incidence of AKI grade 3 multivariable testing was not possible despite the considerable size of this cohort. In 25 of the 27 patients that suffered from AKI grade 3, the AKI was potentially caused by dehydration, which likely confounded our results.

Patients that received chemoradiation (with cisplatin) to treat head/neck cancers were overrepresented in the group of patients that experienced AKI grade 3 (52%). In this subgroup the incidence of mucositis, which lowers fluid intake and therefore is a causal factor for dehydration, is much higher. This underlines the plausibility that AKI grade 3 in most of the patients was caused by dehydration.

The COMT 1947 G>A and c.615+310 C>T SNPs were not associated with AKI grade 3.

Conclusion

This study showed that variation in COMT c.616+367 C>T (rs9332377) potentially affects the development of AKI grade ≥3, although these results appear to be confounded by dehydration. Therefore, the value of this finding for daily practice is currently unclear and needs to be explored in a prospective setting. This study does not provide a rationale for pre-emptive genotyping of COMT SNPs to prevent AKI.

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Influence of cow's milk on the absorption and exposure of erlotinib in NSCLC patients

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Introduction

Erlotinib is an oral EGFR tyrosine kinase inhibitor used in NSCLC. Drug absorption depends largely on its solubility in the stomach and gastrointestinal tract. Potentially, erlotinib -as lipophilic drug- is ought to dissolve better in a fatty drink such as full cow's milk compared to water. Gastric acid reducing agents like proton pump inhibitors (PPIs) decrease the solubility and thus the uptake of erlotinib. Hence, we hypothesized that administration of cow's milk may be a feasible way to increase erlotinib uptake (both with or without PPI co-administration). We performed a two-period randomized cross-over study to investigate the influence of full cow's milk compared to water on the exposure of erlotinib with and without the PPI esomeprazole in NSCLC patients.

Methods

During 24 hours, pharmacokinetic sampling (PK) was performed at days 7 and 14. In the 7 days prior to PK, erlotinib was taken daily with either 250 mL water or full cow's milk. Patients were assigned whether to receive erlotinib with (arm A) or without esomeprazole (40mg qd; arm B) 3 hours prior to erlotinib intake starting 3 days prior to PK. Primary endpoint was change in geometric mean for the area under the curve (AUC0-24h). A linear mixed model was used to analyze AUCs and maximal concentration (Cmax).

Results

Twelve of the 20 patients used erlotinib without a PPI. Erlotinib AUC0-24h decreased non-significantly with 5% (95%CI: -14 to +5%; P=0.3) when administered with milk compared to water in the non-PPI patients. Also in the 8 patients who did use esomeprazole, erlotinib AUC0-24h did not differ between intake with water or milk (95%CI: -29 to +40%; P=1.0). Cmax did not differ in non-PPI users (P=0.6) and in PPI users (P=0.9). However, esomeprazole decreased erlotinib AUC0-24h with 48% (95%CI: -61 to -31%; P<0.001) and Cmax with 55% (95%CI: -66 to -42%; P<0.001) in 7 patients who completed both arms. No differences in toxicities were observed.

Conclusion

Exposure to erlotinib did not change by erlotinib intake with milk compared to water in both the PPI and non-PPI patients. Therefore, the combination with milk instead of water is safe and well tolerated. Esomeprazole strongly decreased both erlotinib AUC0-24h and Cmax, and should be avoided if possible.

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Population pharmacokinetic model of irinotecan and its four main metabolites in patients treated with FOLFIRI or FOLFIRINOX regimen

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Background: Irinotecan (CPT-11) is an anticancer drug included in first-line treatments for patients with metastatic colorectal cancer and pancreatic cancer in combination with leucoverin, 5-fluorouracil (FOLFIRI) and oxaliplatin (FOLFIRINOX). CPT-11 is a prodrug which is converted into the cytotoxic form, SN38 (7-Ethyl-10-hydroxy-camptothecin), by carboxylesterases in the liver and into two inactive forms, APC (7-ethyl-10-[4-N-(5-aminopentanoicacid)-1-piperidino] carbonyloxycamptothecin) and NPC (7-ethyl-10-[4-(1-piperidino)-1-amino]-carbonyloxycampto-thecin) by CYP3A4/5 [1]. SN38 is detoxified by UGT1A1 into SN38G (glucuronidated SN38), an inactive metabolite, before biliary excretion. The aim of this study is to determine the population pharmacokinetic (PK) parameters of CPT-11 and its four main metabolites in metastatic colorectal cancer patients treated with FOLFIRI and FOLFIRINOX regimens and quantify and explain their inter-individual variability.

Methods: A multicenter study of 109 metastatic colorectal cancer patients treated with FOLFIRI and FOLFIRINOX regimen was conducted. 506 plasma samples were collected at five different times during the first cycle of treatment. Plasma concentrations of CPT-11 and its metabolites were measured by high-performance liquid chromatography-fluorescence method [2]. Population PK analysis was performed using Monolix2019R1 software. Model selection and qualification were performed by both statistical and graphical methods. Once the compartmental and random effects models were selected, covariates were tested to explain the inter-individual variability in PK parameters.

Results: A three-compartment model was selected to describe CPT-11 PK with three first-order rate constants for CPT-11 elimination, transformation into SN38 and into APC and a Michaelis-Menten kinetics for transformation into NPC. Two-compartment model was chosen for the PK of SN38 metabolite with a first order rate constant for the conversion of SN38 into SN38G. A one-compartment model with first-order elimination best described SN38G, APC and NPC PK. Residual error was best described by a proportional error model for CPT-11, SN38 and APC and a combined error model for SN38G and NPC. Covariate analysis suggested that the SN38G central volume of distribution is affected by the patient's performance status. Additional covariates were evaluated but not retained: regimen (FOLFIRI/FOLFIRINOX), sex, body surface area, weight, height and comedication with therapeutic antibody.

Conclusion: In FOLFIRI and FOLFIRINOX regimen, CPT-11, SN38, SN38G, APC and NPC were correctly described by our eight-compartmental model. The next step is to establish the relationship between irinotecan PK and its toxicity, taking into account associated drugs (5-fluorouracil and oxaliplatin). This forthcoming PKPD model will allow to perform in silico simulations to define the optimal administration protocol (i.e. dosing, scheduling, sequencing) for a maximal benefit to risk ratio.

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Precision medicine in hematology-oncology: CDA as a predictive marker for Cytarabine exposure in AML patients

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Objectives: Cytarabine (Ara-C) remains the backbone of the vast majority of protocols for treatment of acute myeloid leukemia (AML). We have previously demonstrated that clinical outcome with cytarabine was markedly influenced by genetic polymorphisms affecting CDA, the enzyme responsible for its detoxification to Ara-U in the liver. Interestingly, AML patients with CDA PM phenotype exhibited both high risk of severe/lethal toxicities upon cytarabine treatment, but a trend towards longer progression-free and overall survival as well. We can hypothesize that PM patients had probably higher circulating cytarabine plasma levels and lower circulating plasma levels of inactive Ara-U. To confirm this, we have monitoring drug and main metabolite level. The monitoring cytarabine concentrations in plasma required highly sensitive bioanalytical methods especially during induction phase with low dose cytarabine. We have developed a new LC-MS/MS method that meets these requirements.

Methods: Ara-C and Ara-U concentrations were determined in plasma samples using a new LC-MS/MS method. Blood samples were withdrawn from 7 patients treated for AML with 200mg/m2 Ara-C at as part of a study approved by the institutional review board of the Conception Hospital (Marseille, France) registered as # 2017-A00070-53. Patients were phenotyped for CDA status prior to starting the infusion following a spectrophotometric method previously described and categorized as Poor Metabolizer (PM) or Extensive Metabolizer following CDA activity. Patients were sampled at the end of the administration, then 5 min, 10 min, 1H, 2H and 6H after the end of the infusion.

Results: 4 patients were CDA deficient (i.e., CDA ≤ 2 U/mg, aka PM), and 3 patients were CDA no-deficient (i.e., CDA > 2 U/mg, aka EM). For Ara-C, AUCs were 3312 ± 326 ng/ml.min and 1502 ± 497 ng/ml.min, for PM and EM patients, respectively. The difference was statistically different ($p>0.024$, t test). For Ara-U, AUCs were 7.3.105 ± 2.1.105 ng/ml.min and 4.8.105 ± 0.8.105 ng/ml.min, for PM and EM patients, respectively. The difference was not statistically different ($p>0.05$, t test). Metabolization ratio between AUC of Ara-C and AUC of its metabolite Ara-U was calculated. The mean metabolization ratio was 255 ± 103 and 460 ± 218 for PM and EM patients, respectively. The 1.8-fold difference was not statistically different ($p>0.05$, t test).

Conclusions: This method was successfully applied to determine the pharmacokinetic profile of Ara-C and Ara-U in 7 patients and evidenced marked differences in both drug levels and metabolic ratio depending on patient's CDA status. CDA status could be further used as a covariate to tailor durg dosage so as to ensure an optimal efficacy/toxicity balance in patients with AML. Evaluation of Ara-C pharmacokinetics as part of a prospective clinical trial is currently ongoing

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Application of the Optimal Design Approach to improve Therapeutic Drug Monitoring of Busulfan in Children receiving Hematopoietic stem cell transplantation (HSCT)

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Objectives: Busulfan is the most commonly used agent in Hematopoietic stem cell transplantation (HSCT) conditioning regimes, given alone or in combination. Considerable inter-patient variability exists in the effectiveness and toxicity of busulfan-containing conditioning regimens. Therefore, personalizing Busulfan doses improves the clinical outcomes, and it is clinically accepted due to a narrow therapeutic window. The objective of this study was to find a design that minimizes the uncertainty of population parameters used for busulfan dose prediction.

Methods: Data on 72 patients receiving Busulfan prior an HSCT (7 months-18 years, 5.1–47.0 Kg), suffering from immunodeficiencies or malignant diseases, was used to build a 2 compartment pharmacokinetic (PK) model of the drug. Busulfan (1-2 mg/Kg) was administered intravenously in a 2 or 3-hour infusion for four days prior HSCT, either every day, twice daily or every 6 hours. Blood samples to determine busulfan concentration in plasma were obtained prior the first administration, and 5, 10 and 30 minutes, 1, 2 and 4 hours after the end of the infusion. Once the PK model was built, a distribution of the population parameters was used in the optimization as prior information. The software PopED was used to perform optimal design of the sampling schedule. The covariates included in the PK model were taken into account in the optimization exercise (weight affecting the dose and the all the PK model parameters and age, affecting clearance).

Results: The optimized design considered the three different administration schedules of busulfan, so there is only one protocol of sampling extraction independently from busulfan administration schedule. The optimized sample times that rendered best performance than the protocol times were: 15 minutes after the administration of the drug, and 5 minutes, 35 minutes, 1 hour and 45 minutes after the end of the infusion, and the last sample right after the next administration. Therefore, the new design represents a 16.6 % reduction (n=1) in sampling demanding with respect the current protocol. The efficiency of the optimized design with respect to the protocol was calculated to be 2.84, indicating significantly better performance of optimized design.

The expected Residual Standard Errors (RSE%) of the parameters under the optimal designs were compared to the RSE% of the protocol, showing a reduction from 1 to 27% RSE in the parameters. In addition, prediction performance of the optimized design was evaluated, obtaining similar parameter precision compared to the protocol (maximum bias <10 %).

Conclusions: An optimized sample times design for monitoring busulfan in pediatric patients under HSCT was developed. The evaluation of the reduced design suggests better performance than the original protocol, even reducing the samples per patient. We firmly believe that this work is of potential implementation in the clinical setting, improving patient care.

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Influence of probenecid on the pharmacokinetics and pharmacodynamics of sorafenib

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Background:
Cutaneous adverse effects, like the hand-foot skin reaction (HFSR), are among the most frequently (34% all-grade) observed toxicities with multi-kinase inhibitors such as sorafenib. The exact pathogenesis remains unknown, but prior studies have demonstrated that accumulation of sorafenib in keratinocytes is mediated by the transporter OAT6 (SLC22A20). Therefore we investigated the influence of probenecid on systemic sorafenib pharmacokinetics and tested the hypothesis that the OAT6 inhibitor probenecid decreases the uptake of sorafenib in the skin.

Methods:
Pharmacokinetic sampling was performed in patients on steady state sorafenib treatment at days 1 and 15 of the study through repetitive blood (9 samples during 12h) and skin biopsy collection. Patients received sorafenib (200-800mg q.d.) in combination with probenecid (500 mg BID) on days 2-15. Primary endpoint was Area under the curve (AUC0-12h). Difference in geometric mean AUC with and without probenecid in both plasma and skin samples was tested using a paired t-test. Furthermore difference in other pharmacokinetic parameters and toxicity was determined.

Results:
Probenecid decreased sorafenib AUC0-12h significantly by 35.9% (90%CI: -47.6% to -21.7%; P<0.01). Furthermore peak (-33.1%; 90%CI: -44.3% to -19.7%; P<0.01) and trough levels of sorafenib also decreased (-41.1%; 90%CI: -54.6% to -23.5%; P<0.01). The metabolic ratio of sorafenib-glucuronide (S-glu) to parent drug increased (+27%) i n the presence of probenecid, suggesting a reduction of enterohepatic recirculation. This was supported by our finding that probenecid inhibits OATP1B1, the major hepatocellular uptake carrier of S-glu, at clinically-relevant levels (IC50, ~60 µM). Importantly, sorafenib concentrations in skin biopsies were decreased by 32.5% (90%CI: -52.2% to -4.9%, P=0.07) in the presence of probenecid. There was no clear difference in toxicity, especially in HFSR, between the two treatment arms.

Conclusion:
This study showed a significant decrease in sorafenib and sorafenib metabolite exposure when coadministered with probenecid compared to sorafenib monotherapy. Therefore it may demonstrate proof-of-concept that sorafenib levels in skin can be reduced by pretreating with the OAT6 inhibitor probenecid however systemic sorafenib exposure decreased in the same extent. An effect of probenecid on sorafenib toxicity, especially HFSR, could not be identified in this study. The exact mechanism of this pharmacokinetic interaction is unknown but possibly involves interference with enterohepatic recirculation due to an effect on hepatocellular processing of the metabolite S-glu.

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Population pharmacodynamics modelling of circulating lymphocyte count over time in chronic lymphocytic leukemia patients under ibrutinib treatment

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Background
Chronic lymphocytic leukemia (CLL) is the most frequent leukemia in adults. It is characterized by the accumulation of non-functional B-cells in bone marrow, lymphoid tissues and blood. Ibrutinib is a tyrosine kinase inhibitor used for the treatment of CLL. It targets the BTK protein which is involved in the B-cell antigen receptor. Ibrutinib has several anti-leukemic effects on the lymphocytes: anti-proliferative, egress from lymph nodes, inhibition of re-homing to niches and death in blood and niches. Circulating lymphocyte count over time is an important clinical indicator in CLL. Patients can be divided into three groups of response: inexistent, transitory and prolonged lymphocytosis. Several studies show a trend towards better long-term prognosis for the last group. The objective of this work was to develop a population pharmacodynamics (PD) model describing circulating lymphocyte dynamics under ibrutinib treatment, to assess the influence of pharmacokinetics (PK) on PD response and to explore correlations between PD posthoc parameters and patients' clinical outcome.

Material & Methods
Patients treated with ibrutinib were included in a clinical study and followed up for two years. A total of 7 hospital visits with clinical and biological examinations (including circulating lymphocyte count) were performed. Population models including pharmacokinetics (PK-PD) or not (PD) were tested. For PK-PD models, we used a population PK model of ibrutinib and its main metabolite, dihydrodiol-ibrutinib, which we previously developed and externally validated [1]. The structures of the tested models were based on physiological knowledge of lymphocyte dynamics and ibrutinib effects. Association between PD posthoc parameters and clinical outcome (continuation or not of ibrutinib therapy one year after treatment initiation) was evaluated. Patients were divided into 3 groups: ibrutinib continued, ibrutinib stopped due to adverse event (toxicity) and ibrutinib stopped due to disease progression (inefficacy). Models were developed in NONMEM.

Results
A total of 77 patients and 506 observations were available. The number of patients with inexistent, transitory and prolonged lymphocytosis was 31, 21 and 25 respectively. So far the model that allowed the best description of all types of profiles was a population PD model. It was composed of two compartments: one for lymph nodes and one for blood circulation. Lymphocytes proliferate in lymph nodes (Kprol), are released in blood circulation (Kout) where they die (Kdeath). Baseline lymphocyte count was estimated in both compartments (Base1, Base2). Because after some time lymphocyte count stabilizes to a plateau, we

added an offset term to the blood compartment. Proportional residual variability was 25%. No association between PD parameters and ibrutinib discontinuation one year after treatment initiation was found.

Conclusion

The first nonlinear mixed-effects PD model describing lymphocyte dynamics under ibrutinib treatment was developed. The final model fits the observed data well for all types of profiles. The structural model is concordant with physiological processes. No association was found between PD posthoc parameters and discontinuation of ibrutinib therapy one year after its initiation. Influence of PK on PD response, association with other clinical outcomes (e.g. PFS) and influence of covariates on PD parameters will be further explored.

[1] Gallais F. et al. Population pharmacokinetics of ibrutinib and its dihydrodiol metabolite in patients with lymphoid malignancies. Poster PAGE 2019.

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Modulation of CYP3A activity to increase the oral bioavailability of ibrutinib

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Background:
Ibrutinib (Imbruvica; PCI-32765), an orally administered inhibitor of Bruton's tyrosine kinase, is considered a breakthrough targeted therapy that is approved as frontline therapy in chronic lymphocytic leukemia (CLL). Ibrutinib has an average oral bioavailability in humans of <4% and exhibits substantial variability in exposure, which predisposes patients to unpredictable and potentially harmful adverse events such as bleeding and atrial fibrillation. As ibrutinib is subject to extensive first-pass metabolism by CYP3A following oral administration, inhibition of CYP3A activity may be a promising strategy to decrease interindividual pharmacokinetic variability. The objective of this study was to characterize the impact of CYP3A on the pharmacokinetics of ibrutinib and its main active metabolite, PCI-45227, in mice.

Methods:
To characterize the impact of CYP3A on ibrutinib disposition, in vivo pharmacokinetic studies were performed in wild-type (WT) male and female FVB mice treated with CYP3A inhibitors including ketoconazole (50 mg/kg p.o.) and cobicistat (30 mg/kg; p.o.) or the respective vehicle controls (PEG400 or corn oil p.o.) thirty minutes prior to dosing with ibrutinib (10 mg/kg p.o.). Based on these results, CYP3A(-/-) female FVB mice were treated with ibrutinib (10 mg/kg p.o. or 1 mg/kg i.v.) alone or thirty minutes after dosing with cobicistat (30 mg/kg; p.o.). Concentrations of ibrutinib and PCI-45227 in plasma were determined by a validated method based on liquid chromatography-tandem mass spectrometry, and pharmacokinetic parameter estimates were calculated with the software package Phoenix WinNonlin (Version 8.1). Student t-tests comparing mean AUC values between groups were used to determine significance.

Results:
The peak plasma concentration (Cmax) and the area under the curve (AUC) of ibrutinib were ~2-fold higher in female mice compared with male mice, suggesting that the pharmacokinetic profile of ibrutinib exhibits sexual dimorphism. Administration of pharmacologic CYP3A inhibitors prior to ibrutinib resulted in a ~10-fold increase in the AUC of ibrutinib and a substantial decrease in the PCI-45227 to ibrutinib AUC ratio regardless of sex. As expected, when ibrutinib was administered orally to CYP3A(-/-) mice, the AUC of ibrutinib in CYP3A(-/-) mice was increased ~10-fold with almost no formation of the PCI-45227 metabolite compared with WT mice. Cobicistat did not impact ibrutinib AUC in CYP3A(-/-) mice, which suggests that CYP3A inhibition is the major mechanism for cobicistat-induced increases in ibrutinib exposure.

Conclusions:
The current study demonstrates that mice provide a translationally useful model organism to evaluate the potential clinical impact of CYP3A inhibitors on the pharmacokinetics of ibrutinib. Previously obtained data with other kinase inhibitors indicate that patients with high CYP3A4 activity may benefit from an increased dose to achieve drug concentrations required to interact with kinase targets, and a strategy by which enzyme activity is intentionally inhibited could achieve similar results. In view of the significant inverse correlation between decreasing absolute bioavailability and inter-individual pharmacokinetic variability, the current data provide a rationale for the development of exploratory clinical studies aimed at decreasing the

variability in ibrutinib exposure by concomitant administration of CYP3A inhibitors. Future preclinical efficacy studies will determine the impact of this strategy on outcomes in models of disease.

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Screening for Potential Drug Interactions of TKIs with OATP1B1

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Background

Tyrosine kinase inhibitors (TKIs) have revolutionized the landscape of cancer treatment shifting the standard of care for many cancers from conventional chemotherapy to the use of individualized therapies based on a cancer's genetics. Despite improving outcomes in both malignant and nonmalignant disease, these agents suffer many of the same issues as conventional chemotherapy including extensive inter-individual pharmacokinetic (PK) variability and a narrow therapeutic window. Combined, these factors make drug-drug interactions (DDI) problematic for TKIs. Moreover, DDIs with TKIs are often unpredictable in part due to a limited understanding of how co-administered drugs impact PK or an incomplete characterization of the PK of TKIs and their metabolites as either victims or perpetrators in DDIs. For example, while antifungal agents such as ketoconazole are largely known for their impact on CYP3A metabolism, some of these agents have been shown to potently inhibit transporters such as OATP1B1. We previously characterized the impact of impaired OATP1B1 function on the disposition of several TKIs, and performed population PK modeling optimize the use of TKIs such as sorafenib to decrease the incidence of toxicities. We previously found that co-administration of OATP1B1 inhibitors significantly alters the clearance of sorafenib and its main metabolite, sorafenib-glucuronde. In the present investigation, we sought to characterize the OATP1B1 inhibitory potential of medications frequently co-administered with TKIs.

Materials & Methods

We screened the OATP1B1 inhibitory potential of various medications commonly administered together with TKIs, and also considered TKIs as perpetrators. Based on the medications that were co-administered in a recently completed clinical trial with sorafenib, we evaluated vancomycin and several antifungal drugs (ketoconazole, posaconazole, voriconazole and micafungin). We also screened probenecid, cobicistat and rifampin, an antibiotic known to potently inhibit OATP1B1, as well as the TKIs ibrutinib, gilteritinib, and an investigational drug candidate, TP-0903. We used a stably transfected HEK293 cell line recombinantly expressing OATP1B1 to analyze the uptake inhibition of the model substrate, estradiol 17beta-d-glucuronide (EβG). Inhibitor concentrations of 10 µM were used to screen inhibitory potential before conducting further concentration-dependent analyses. Statistical analysis was performed with two-tailed t-test, and $P<0.05$ was considered statistically significant.

Results

Of the compounds screened, micafungin, ketoconazole, posaconazole, cobicistat, ibrutinib, gilteritinib and TP-0903 all inhibited uptake of EβG by OATP1B1 by more than 50%. Further analysis of probenecid, which can circulate at plasma concentrations exceeding 10 µM, indicated that probenecid also potently inhibited OATP1B1 at physiologically relevant concentrations (IC50=118 µM). Together, these findings helped inform the covariate design of our sorafenib population PK model.

Conclusion

In the present study, we demonstrated a novel mechanism underlying DDIs between several co-administered medications, including those (e.g. micafungin) that were not previously thought to impact the

disposition and clearance of sorafenib, and observed that several TKIs themselves affect OATP1B1 function. Future studies will determine the inhibitory potential of these medications across disparate OATP1B1 substrates and a gradient of concentrations of those substrates. Depending on these findings, future in vivo studies will utilize mice with a deficiency of the human orthologue OATP1B2 to characterize the physiological relevance of these DDIs.

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Effects of dietary restriction in cancer patients receiving irinotecan.

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Background
Irinotecan is widely used, but also known for its severe toxicities neutropenia and diarrhea. Based on preclinical data, combined caloric and protein restriction (CCPR) might improve treatment tolerability without impairing antitumor effect. Therefore, we studied the influence of CCPR on irinotecan pharmacokinetics and toxicity.

Methods
In this cross-over trial, patients with liver metastases of solid tumors were included and randomized to treatment with irinotecan preceded by 5 days of CCPR (~30% caloric and ~70% protein restriction) during the 1st cycle and a 2nd cycle preceded by a normal diet (ND) or vice versa. During both cycles, 24-hours blood sampling was performed and 24-26 hours after infusion biopsies of both healthy liver (HL) and liver metastasis (LM) were taken. Primary endpoint was the relative difference in geometric means for the active metabolite SN-38 concentration in HL, as analyzed by a linear mixed model. Secondary endpoints included irinotecan and SN-38 concentrations in LM, plasma area under the curve (AUC0-24h), and toxicity.

Results
Interpatient variability (n=19) in tissue irinotecan and SN-38 concentrations was high, showing no significant differences in irinotecan (+16.8%, 95% CI: -9.7-51.1%, P=0.227) and SN-38 (+9.8%, 95% CI: -16.4-44.2%, P=0.48) concentrations between CCPR and ND in HL, as well as in LM (irinotecan: -38.8%, 90% CI: -59.3:-7.9%, P=0.05 and SN-38: -13.8%, 90% CI:-40.7-25.4%, P=0.50). CCPR increased irinotecan plasma AUC0-24h with 7.1% (95% CI: 0.3-14.5%, P=0.04) compared to ND, while the SN-38 plasma AUC0-24h increased with 50.3% (95% CI: 34.6-67.9%, P<0.001). CCPR was well tolerated with low incidence of grade ≥3 therapy related toxicity. Grade ≥3 toxicity was not increased during CCPR vs ND (P=0.69). No difference was seen in neutropenia grade ≥3 (47% vs 32% P=0.38), diarrhea grade ≥3 (5% vs 21% P=0.25), febrile neutropenia (5% vs 16% P=0.50) and hospitalization (11% vs 21% P=0.634) during CCPR vs ND.

Conclusions
CCPR resulted in a dramatically increased plasma SN-38 exposure, while toxicity did not change. CCPR did not result in altered irinotecan and SN-38 exposure in HL and LM. CCPR might therefore potentially improve the therapeutic window in patients treated with irinotecan.

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Comparison of intratumoral docetaxel exposure in cancer patients between nanoparticle entrapped docetaxel (CPC634) and conventional docetaxel (Cd): the CriTax study

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Background
Ineffective chemotherapy may partly be caused by subtherapeutic intratumoral drug levels. Nanomedicines are developed to improve the therapeutic index, by increasing intratumoral drug exposure and preserving healthy tissue. CPC634 is a new nanoparticle entrapping docetaxel. Here, we hypothesized that CPC634 increases intratumoral docetaxel level and overall duration of exposure.

Methods
In this randomized cross-over study we assessed both plasma and intratumoral pharmacokinetics (PK) of docetaxel after intravenous administration of 75 mg/m2 conventional docetaxel (Cd) and CPC634. We aimed to identify a 25% increase of intratumoral docetaxel exposure after CPC634 infusion compared to Cd. Adult patients were randomized to receive Cd in cycle 1 and CPC634 in cycle 2 or vice versa. Tumor biopsies were taken 24, 48, 72, 96, 168 or 336 hours after infusion during both cycles. Total docetaxel concentration (TDC) was determined for both drugs and released docetaxel for CPC634 in tumor tissue and plasma. PK data were analyzed using mixed modeling.

Results
In total, 21 evaluable patients were included. In plasma, the area under the curve (AUCinf) of released docetaxel was higher (+27%, 95% CI: 11-44%, P=0.001) while peak plasma concentration (Cmax) (-91%, 95% CI: -92:-89%, P<0.001) and clearance (-21%, 95% CI: -31;-10%, P=0.001) decreased during CPC634 administration versus Cd.
Intratumoral TDC was 375% higher (95% CI: 187-686%, P<0.001) after CPC634 administration, while released docetaxel was comparable to Cd (+8%, 95% CI: -30-+69%, P=0.71).

Conclusions
The plasma PK profile of CPC634 is favorable compared to Cd since a lower Cmax, lower clearance and prolonged higher systemic exposure is seen. Higher intratumoral TDC levels were reached with CPC634, while released docetaxel levels were comparable to Cd.
The almost 4-fold increased tumor accumulation for prolonged period of time of TDC supports the expectation that CPC634 will exhibit beneficial efficacy/safety balance.
Additional studies assessing the intratumoral exposure to CPC634 (NCT0371243) and a phase II efficacy study of CPC634 in platinum resistant ovarian cancer patients (NCT03742713) are currently ongoing.

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Prediction of Capecitabine induced Severe Toxicity using Machine Learning Techniques

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Background: The 5-Fluorouracil (5FU) prodrug known as Capecitabine (Xeloda®) is an anti-cancerous used in chemotherapies for solid tumor. This medicine's metabolite is an uracil similar, part of the fluoropyrimidine family and is used in the treatment of digestive and mammary adenocarcinomas. It is also used in colorectal cancer and other carcinomas. It belongs to the antimetabolites group of medicines as a pyrimidine analogue. 5FU acts as an inhibitor of the thymidylate synthase enzyme, which blocks the synthesis of the thymidine required for DNA replication. Dihydropyrimidine dehydrogenase is the rate-limiting enzyme responsible for 80-85% of 5FU catabolism while 5-20% of the 5FU is being eliminated in the urine. DPD deficient patients are more likely to present severe toxicity as the 5FU will accumulate in their body.

Materials & Methods: Patients with breast cancer were treated with oral 5FU prodrug (Capecitabine) as monotherapy. Age, BSA, uracil blood rate and the ratio between dihydrouracil and uracil blood rates were recorded before the first Capecitabine cycle. We developed a machine learning analysis using gradient boosting regression and random forest classifier techniques to compute dynamic models that predict Capecitabine toxicities with respect to the uracil blood rate dosage. Several regression parameters were optimized using a grid search technique. To validate models' accuracy, we performed a cross-validation and compared predicted and observed probabilities of severe toxicities.

Results: Classification algorithms were compared in their ability to differentiate low and severe toxicities. The best result was achieved using a random forest classifier which accuracy was 93.8% on the test dataset. The severe toxicity probability was modeled using an optimized gradient boosting tree regressor. The comparison between the observed and predicted probabilities was very good. Using statistical tests, it has been shown that a statistically significant difference ($p = 0.021$) in chances of severe hematological toxicities exists between groups of patients separated using an uracil blood rate value of 16 ng/mL.

Conclusions: In the attempt to anticipate the occurrence of severe toxicities in patients treated with Capecitabine, we have computed machine learning based models that predict the probability of severe toxicity (hematological and digestive) as function of the patient's uracil blood rate which is a good predictive marker according to the experts and the results of our statistical tests.

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Pharmacokinetics and safety of pazopanib in frail elderly patients.

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Background

Pazopanib is a multi-kinase inhibitor approved for the treatment of renal cell carcinoma and soft tissue sarcoma. The primary objective of the VOTRAGE clinical trial (NCT 01642017) was to determine the maximum tolerated dose (MTD) of pazopanib in a population of frail elderly patients (over 75 years old and in group 2 classification of the International Society of Geriatric Oncology). A pharmacokinetic (PK) data analysis of pazopanib was performed to evaluate the influence of age.

Materials & Methods

Patients were recruited at different sequential dose levels from 400 mg to 800 mg QD, according to a 3+3 design. Patients were sampled at day 0 (1, 2, 4, 6, 8, 12, and 24 hours post-administration) and day 15 (pre-dose, 2 hours, and 4-8 h intervals). Pazopanib concentrations were assessed by means of a validated liquid chromatography – tandem mass spectrometry method. Additional PK data from two previous phase I studies conducted in younger patients were pooled with concentration data of the VOTRAGE study. Pooled data was analyzed with NONMEM 7.4 with a structural model adapted from Yu et al [Clin Pharmacokin, 2016]. This model can take into account a relative bioavailability (rF) that decreases with time and dose. Age was tested as a covariate on PK parameters with inter-individual variability (IIV).

Results

Eighteen patients, median age 82.5 years (range 75 – 91), were included in the VOTRAGE study, and 172 pazopanib plasma concentrations were measured. Final dataset was composed of 1,073 concentrations obtained from 74 patients, median age 65 years (range 25 – 91). The structural model was identical to the one developed by Yu et al, except the dose-dependent decrease of rF that could not be reproduced due to the small range of dose administered in our study (400 – 800 mg QD). Inter- (IIV) and intra-individual variability for rF was, respectively, 38% and 42%. IIV for clearance (CL) was 43 %. Age was a significant covariate of CL, as the latter decreased in older patients, but did not influence oral clearance (CL/rF) nor exposure to pazopanib, due to a trend of lower rF in older patients. Patients with proton-pump inhibitors displayed a significantly higher CL/rF. The MTD has been 600 mg daily since dose-limiting toxicities were experienced at dose level 3 (800 mg daily) for three out of five patients. Overall, a significant relationship was observed between pazopanib daily exposure and toxicity.

Conclusions

Pazopanib should be initiated at 600 mg daily in frail elderly patients. Our study confirms the high IIV pazopanib PK. It reinforces the interest for detecting drug-drug interactions, especially with antacids, and

the rationale to perform therapeutic drug monitoring in order to control pazopanib exposure, despite the intra-individual PK variability.

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Comprehensive Pan-Cancer analysis of somatic mutations in drug transporters to reveal acquired and intrinsic drug resistance in 3149 metastatic cancer patients

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Background

Intratumoral genetic changes are known to induce drug resistance at pharmacodynamic level. We hypothesize that somatic point mutations, small indels, copy number variations (sCNV) and/or structural variations in genes encoding drug transporters can also cause pharmacokinetically-mediated drug resistance. We aimed to quantify the incidence of these somatic aberrations.

Methods

We interrogated whole-genome sequencing (WGS) data from a Dutch pan-cancer cohort of metastatic cancer patients (N = 3149 at ~118x and matched peripheral blood at~38x read depth). Previous systemic treatment has been given to 55% of patients. Somatic aberrations (germline filtered) were analyzed in drug transporters (N=51), present on the Drug Metabolizing Enzymes and Transporters (DMET™ plus) panel (v.32). Enrichment of somatic variants was estimated by assessing nonsynonymous/synonymous mutation ratio deviations (dN/dS) and sCNV were detected with GISTIC2.

Results

In total, 3156 somatic variations in genes encoding drug transporters were observed in 1055 patients (33.5%). Focusing on coding mutations, 1489 somatic variants were observed in 690 patients (21.9%) of whom 93.2% were systemically pretreated (51.7% of patients also received radiotherapy pretreatment) and 6.8% only received radiotherapy pretreatment. The variations were predominantly nonsynonymous SNVs (N=1066). In 13 patients, we found a total of 20 somatic mutations (i.e. not present at germline) that were identical to SNP variants on DMET™ plus.

Coding germline variants, in at least one of the drug transporter genes, were present in 93.3% of the patients.

Somatic copy number variations (N=3099; 2484 deep gene-level gains and 615 deletions) were observed in 1047 patients (33.2%). While deep sCNVs tend to show a clear direction (exclusively amplified or deleted)

for most transporter genes pan-cancer, none of the 51 drug transporters were found to be more significantly affected in any of the treatment groups.

Conclusions

In the largest metastatic pan-cancer WGS cohort worldwide, we characterized the pharmacogenomic drug transporter landscape in tumor cells as a potential mechanism of drug resistance. The functional and clinical consequences of these aberrations need to be studied prospectively.

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Population pharmacokinetic model of sorafenib and application to therapeutic drug monitoring

Mr. Ba Hai LE[1,2], Mrs Nadège NEANT[1], Mr Benoit BLANCHET[3], Mr François Goldwasser[3], Mr Joseph CICCOLINI[1], Mrs Florence GATTACCECA[1]

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Introduction: High inter- and intra-individual variabilities (61-65% and 44-47% respectively) of pharmacokinetics (PK) of sorafenib were observed during phase I studies, as well as in some population pharmacokinetic (pop-PK) studies, which could explain the unstable response and the unintended toxicities that occur in some patients under a recommended dosage of sorafenib [1-4]. Therefore, we aimed to develop a sorafenib pop-PK model based on a large population treated by sorafenib during a long period. This pop-PK model was then used to predict sorafenib individual plasma PK based on sparse therapeutic drug monitoring using Bayesian approach, then to explore the relationship between sorafenib plasma exposure and toxicity outcome in patients from La Timone hospital.

Method: Sparse PK data available from 267 patients treated with sorafenib between 2008 and 2018 have been included in this multicentric study (10 French hospitals). The PK data were analyzed using nonlinear mixed-effect modeling (NONMEM software version 7.3). Model evaluation was performed using standard goodness-of-fit plots, and simulation-based tools such as visual predictive check (VPC).

The final pop-PK model was applied, using Bayesian method in NONMEM, to estimate the individual pharmacokinetic parameters of 23 patients based on 1 or 2 blood samples collected from therapeutic drug monitoring at La Timone hospital (Marseille). The PK of sorafenib over the course of the treatment was simulated in R studio for each patient.

Results: 1310 plasma concentrations collected at steady-state were available to build the model. The follow-up of patients lasted between 15 and 1997 days (5.5 years). A 1-compartment structural model with first-order absorption and linear elimination described the data satisfactorily. Bioavailability (F1) was found to vary as a function of the dose and to decline over time on sorafenib treatment. Typical values (RSE %) of the final model parameters were as follows: clearance (CL) 1.41 L/h (9.4%), distribution volume (V) 50.3 L (21.1%), absorption rate constant (ka) 0.635 h-1 (35.9%). The high inter-patient variability was confirmed in this study with 44.4 % for CL (46.5%), V (93.7%) and ka (100% fixed). The lack of information regarding the absorption phase and covariates such as food intake may account for the extremely large variability of ka. Overall 27 sparse sorafenib concentrations (2.5-384 hours after intake sorafenib) of 23 patient who were treated with sorafenib were collected as well as toxic events. Relationship between simulated exposure and toxicity was assessed. Virtual therapeutic drug monitoring scenario were compared.

Conclusion and perspectives: The high unexplained inter-individual variability in our population could be partly explained by covariates that will need to be collected in further prospective studies. However, the established population model allows reliable prediction of individual PK based on Bayes estimation. The population model could be used in the context of therapeutic drug monitoring to support dose adjustments in patients.

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Population pharmacokinetic and pharmacogenetic analysis of mitotane in adrenocortical carcinoma patients: towards individualized dosing

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Background: Mitotane, a highly lipophilic compound with an extremely long half-life, is the only agent approved for the treatment of adrenocortical carcinoma (ACC). To ensure treatment efficacy and avoid toxicity, mitotane plasma concentration is advised to be maintained between the therapeutic range of 14-20 mg/L, which requires therapeutic drug monitoring (TDM). However, the lack of ability to predict mitotane plasma concentrations may result in a suboptimal time period to reach the therapeutic window or unexpected toxicity. In this study, we aim to develop a population pharmacokinetic (PopPK) model to characterize and predict the pharmacokinetics (PK) profiles of mitotane in ACC patients, as well as to explore the effect of pharmacogenetic polymorphisms on mitotane clearance. Ultimately, we aim to facilitate mitotane dose optimization and individualization for ACC patients.

Methods: Routine mitotane TDM trough concentration data, as well as a limited amount of intensive sampling data, was collected retrospectively from patients diagnosed with ACC from the Dutch Adrenal Network. Patients received mitotane tablet orally. PopPK modelling analysis was performed with NONMEM (version 7.4.1). Data below the quantification limit was omitted. Inter-occasion variability (IOV) of apparent systematic clearance was included. Absorption rate constant was first estimated based on the data of patients who contributed drug absorption information and then fixed to analyses the full dataset. Genotypes of SNPs included in the DMET™ plus array (Affymetrix UK Ltd), patients' demographic information, and clinical characteristics were investigated as covariates. After obtaining and evaluating the final model, simulations were performed for optimizing treatment regimens for included patients.

Results: A two-compartment model with first-order absorption and elimination best described the PK data of mitotane collected from 48 patients. Lean body weight (LBW), genotypes of rs4244285 (CYP2C19), rs4149057 (SLCO1B1), and rs7311358 (SLCO1B3) were identified to affect mitotane clearance significantly and clinically relevant. Fat amount (i.e. weight – LBW) was identified to affect the central distribution volume significantly. The predictability and stability of the model were confirmed to be acceptable. Protocols that shorten the period to reach the therapeutic target while limiting the risk of toxicity were established.

Conclusions: The current study developed a two-compartment PopPK model which well characterized mitotane PK profiles in ACC patients. The pharmacogenetic polymorphisms of rs4244285 (CYP2C19), rs4149057 (SLCO1B1), and rs7311358 (SLCO1B3), as well as LBW and fat amount, can be used to individualize the initial dose of mitotane. Furthermore, optimal treatment schedules for individual patients can be developed by simulation with the develop PK model. These findings should be validated in a prospective study.

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Developing drug delivery system for ASO in prostate cancer: preliminary results

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Prostate cancer (PCa) is, the second most common cancer in men worldwide and the 5th leading cause of death by cancer. The first-line therapy for advanced PCa is castration chemotherapy but after usually 1-3 years, patients will ultimately become resistant to the therapy (i.e. castration resistance (CR)) and develop metastases. The overexpression of TCTP (Translationally Controlled Tumor Protein) was found to play an important role in CRPCa. In the recent years, antisense technology has emerged as a promising strategy in cancer. The principle of this technology is the sequence-specific binding of an antisense oligonucleotide (ASO) to target mRNA, resulting in the prevention of gene translation. Thus developing an ASO directed against TCTP seems to be an interesting strategy. In this context, developing drug delivery systems appears to be a strategy that can improve the efficacy / toxicity balance of ASO.

In this study, we developed two-dimensional (2D) and three-dimensional (3D) spheroids (low density 2500 or high density 5000 cells) to test the biodistribution and the efficacy of free drugs, ASO-liposome and ASO immunoliposomes anchored with trastuzumab.
Immunoliposomes were synthesized using the standard thin film method and maleimide linker. PC-3 human PCa cell lines were tested as a canonical model for PCa expressing HER-2. 2D cell viability was determined using spectrometric MTT assay. 3D spheroids cell viability was determinate in bioluminescence using luminescent assay.

In 2D, the IC50 for free-ASO was 188.4 +/- 0.1 nM and 260.5 +/- 47.5 nM for free-trastuzumab. Both free-ASO and free-trastuzumab had no efficacy on cell viability in 3D. The non-toxic concentration with empty liposome was defined for 10 nM. Based upon the observations we decided to work for a concentration of encapsulated ASO of 150 nM and 8nM lipids concentration.
Low density PC-3 cells spheroids cell viability were 77 +/- 7% for liposomes and 98+/-2% for immunoliposomes (p=0.479) for a treatment at D3 and were 72 +/- 6% for liposomes and 114% +/-10% for immunoliposomes (p=0.941) for a treatment at D3 and D10. No efficacy appears for high density PC-3 cells spheroids.

Cytotoxicity tests first performed in 2D models allowed determining IC50's of free ASO and trastuzumab and determination of non-toxic liposome concentrations. These values helped us to determine next the concentrations to be used for the 3D testing on spheroids. Using 3D models the antiproliferative activity of free ASO was in line with that already described in the literature, thus confirming the need to cargo ASO to increase its efficacy. Free trastuzumab was not active, and questioned the significance of Her2 expression measurement as a predictive marker for efficacy in this setting. A trend towards antiproliferative activity was observed with ASO-liposome at least in low density spheroids. Conversely immunoliposome showed no activity. Our preliminary results question the importance of HER2 as a target to improve drug delivery in PCa with liposome difference in efficacy between low and high density spheroids suggests an uptake issue. Measuring TCTP expression will help to understand whether weak level of target engagement could explain the results.

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Population pharmacokinetic model of sorafenib and application to a case report

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Introduction: High inter- and intra-individual variabilities (61-65% and 44-47% respectively) of pharmacokinetics (PK) of sorafenib were observed during phase I studies, as well as in some population pharmacokinetic (pop-PK) studies, which could explain the unstable response and the unintended toxicities that occur in some patients under a recommended dosage of sorafenib [1-4]. Therefore, we aimed to develop a sorafenib pop-PK model based on a large population treated by sorafenib during a long period. This pop-PK model was then used to predict sorafenib individual plasma PK based on sparse therapeutic drug monitoring using Bayesian approach, then to explore the relationship between sorafenib plasma exposure and toxicity outcome in patients from La Timone hospital.

Method: Sparse PK data available from 267 patients treated with sorafenib between 2008 and 2018 have been included in this multicentric study (10 French hospitals). The PK data were analyzed using nonlinear mixed-effect modeling (NONMEM software version 7.3). Model evaluation was performed using standard goodness-of-fit plots, and simulation-based tools such as visual predictive check (VPC).

The final pop-PK model was applied to provide explanations for the onset of severe sorafenib-related toxicities in one patient, then to evaluate the rationale of the associated empirical dose reductions in this patient. The individual parameters were estimated using Bayesian method in NONMEM and used to simulate the exposure to sorafenib over the course of the treatment in R studio.

Results: 1310 plasma concentrations collected at steady-state were available to build the model. A 1-compartment structural model with first-order absorption and linear elimination described the data satisfactorily. Bioavailability (F1) was found to vary as a function of the dose and to decline over time on sorafenib treatment. Typical values (RSE %) of the final model parameters were as follows: clearance (CL) 1.41 L/h (9.4%), distribution volume (V) 50.3 L (21.1%), absorption rate constant (ka) 0.635 h-1 (35.9%). The high inter-patient variability was confirmed in this study with 44.4 % for CL (46.5%), V (93.7%) and ka (100% fixed). The lack of information regarding the absorption phase and covariates such as food intake may account for the extremely large variability of ka.

Based on the final pop-PK model, the individual parameters of the patient were estimated and used to describe the PK of sorafenib over the course of the treatment. The steady-state AUC from 0 to 12h (AUC0-12) post dose was calculated: values of 109.4, 82.3 and 78.9 mg*h/L were obtained with the dosages 400mg twice daily, 400mg daily and 200mg daily respectively. These values are particularly high when compared to the mean AUC0-12 of 57.7±28.6 mg* h/L obtained in patients experiencing grade 3–4 adverse events in a previous study [4] and are consequently consistent with the observed severe toxicities. These results document the decision to continue reducing the sorafenib dose by expanding the time between doses with the 200mg dosage.

Conclusion and perspectives: The high unexplained inter-individual variability in our population could be partly explained by covariates that will need to be collected in further prospective studies. However, the established population model allows reliable prediction of pharmacokinetics based on Bayes estimation. The population model could be used in the context of therapeutic drug monitoring to support dose adjustments in patients.

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The impact of renal function on pemetrexed pharmacokinetics: implications for dosing in patients with impaired renal function.

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Background
In the era of combined chemo-immunotherapy, pemetrexed remains a pharmacotherapeutic cornerstone for treatment of lung cancer. Currently, pemetrexed is contra-indicated in patients with a creatinine clearance (CrCl) <45 ml/min. As lung cancer patients are at high risk of renal impairment, effective therapy may be withheld from a substantial part of this patient group. To optimally benefit from pemetrexed-based cancer treatment, safe dosing strategies for these patients should be investigated. Previous pharmacokinetic (PK) studies on pemetrexed did not include patients with impaired renal function. To further explore pemetrexed dose optimization strategies, knowledge of the pharmacokinetics in this patient group is essential. Therefore, the aim of our study was to investigate population pharmacokinetics of pemetrexed in patients with various levels of renal function.

Methods
Phase I pharmacokinetic data of pemetrexed were obtained from Eli Lilly through Clinical Study Data Request (CSDR). The following parameters were collected for each individual: pemetrexed dose, infusion rate, sampling times, pemetrexed plasma concentrations, sex, age, ethnicity, weight, height, body surface area (BSA) and serum creatinine. Using these data, we calculated creatinine clearance (CrCl, Cockcroft-Gault) and estimated glomerular filtration rates (eGFR) as CKD-EPI and MDRD. A population pharmacokinetic analysis was performed using NONMEM V7. Volume of distribution and intercompartmental clearance were allometrically scaled to total body weight, and the different measures for renal function (CrCl, CKD-EPI and MDRD) were tested as covariates for clearance. The covariate with the largest decrease in objective function value (OFV) was retained in the model. Models were assessed using standard goodness-of-fit (GOF) plots.

Results
The final dataset consisted of 47 individuals with various levels of renal function (CKD-EPI range: 14-146 mL/min). A three-compartment model with allometric scaling fitted the data best. Typical values of renal clearance (Cl-r) and non-renal clearance (Cl-nr) (with relative standard error RSE%) were 3.65 L/h (9%) and 0.528 L/h (53%). For central volume of distribution (V1) and peripheral volume of distribution (V2 and V3) typical values with RSE% were 6.85 L (6%), 8 L (6%) and 1.16 L (8%), respectively. Absolute CKD-EPI was included as a linear covariate on pemetrexed clearance in the final model, which reduced the interindividual variability (IIV) on clearance from 39.9% to 21.9%

Conclusions
The presented population pharmacokinetic analysis is the first to include patients with both severe renal impairment and adequate renal function. Compared to the findings of Latz et al. (2006), we found that renal function is more important for pemetrexed clearance. We predict that in a patient with an impaired renal function of 20 mL/min, the clearance of pemetrexed is approximately 50% lower than previously thought. Our findings support that renal function based dosing should be applied for pemetrexed. Together with data

on the pharmacokinetics/pharmacodynamics (PK/PD) of pemetrexed, this model can be used to develop safe dosing strategies for lung cancer patients irrespective of the presence of renal impairment.

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Long term pemetrexed-based cancer treatment leads to nephrotoxicity

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Background
Pemetrexed is widely used as an anti-folate cytostatic agent for the treatment of lung cancer. As it is primarily eliminated by renal excretion, adequate renal function is essential to prevent toxic exposure. Pemetrexed is currently contraindicated in patients with a creatinine clearance <45 ml/min. Lung cancer patients are at risk of developing renal insufficiency due to use of nephrotoxic platinum-based drugs. However, growing evidence suggests that pemetrexed itself may also be nephrotoxic. Maintenance of adequate renal function is a requirement for safe, long-term pemetrexed treatment, either as monotherapy or combined with pembrolizumab. Therefore, the aim of this study was to describe the prevalence of nephrotoxicity and related clinical consequences during pemetrexed-based treatment. The secondary objective was to identify risk factors for the decrease in renal function.

Methods
For this retrospective cohort study, all patients who received at least 1 cycle of pemetrexed-based therapy between January 1st 2014 and February 1st 2019 at the Jeroen Bosch Hospital were identified. Patient demographics were collected, together with relevant information regarding comorbidities, comedication and cancer treatment. For assessment of renal function, serum creatinine measurements at baseline and end of therapy (maximum 28 days after last dose) were used to calculate the estimated glomerular filtration rate (eGFR) according to the CKD-EPI-formula. The primary outcome was the prevalence of a significant decline in eGFR (defined as ≥25% reduction) or cessation of therapy due to nephrotoxicity. For the secondary outcome, multivariate regression analysis with Bonferroni correction was performed to identify possible risk factors for the development of renal impairment during pemetrexed-based therapy.

Results
Of the 359 patients included in this analysis, 21% patients had a significant decline in renal function after treatment and 8.1% of patients discontinued treatment due to nephrotoxicity. Cumulative dose (≥10 cycles of pemetrexed-based therapy) was identified as a risk factor for the primary outcome measure (adjusted OR 5.66 (CI 1.73-18.54)). There was a trend of increasing risk of nephrotoxicity with increasing number of comedications or comorbidities.

Conclusions
This study indicates the association between pemetrexed treatment and renal function decline and showed that the risk for renal function decline increases with the cumulative dose. Renal impairment is expected to become an even greater issue now that pemetrexed-based immunochemotherapy results in longer survival and thus longer treatment duration. Our data call for innovative interventions to maintain the safe and effective long-term treatment with pemetrexed .

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Correlation between sunitinib exposure and toxicity in a real-life patient cohort

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Background: Sunitinib is a tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST) and neuro-endocrine tumors. It is currently administered at a fixed dose in several dosing schedules. Large interpatient pharmacokinetic variability has been described. Retrospective analyses of clinical trials have demonstrated an exposure-response and exposure-toxicity relationship for sunitinib. An upper limit of 75-87.5 ng/ml has been described. However, participants from clinical trials differ substantially from real-world patient cohorts. Therefore, the aim of this study was to investigate the relationship between sunitinib exposure and toxicity in a real-world patient cohort.
Materials & Methods: In this retrospective observational cohort study, patients were included who were treated with sunitinib for RCC or GIST and of whom sunitinib sum (sunitinib + its active metabolite SU12662) trough concentrations (Ctrough) were measured between July 2016 and June 2019 at the Radboud University Medical Centre in Nijmegen, the Netherlands. Since both continuous and intermittent dosing was used, dose-normalized Ctrough levels were calculated in order to compare data. Patients were divided into two groups depending on the occurrence of clinically relevant toxicity, which was defined as toxicity requiring dose reduction. For each patient without clinically relevant toxicity, the geometric mean of the sunitinib sum Ctrough levels was calculated. This was compared to the geometric mean of sunitinib sum Ctrough levels until dose reduction in patients with clinically relevant toxicity. Furthermore, the individual sunitinib sum Ctrough measurements (each measurement regarded independently) directly prior to dose reductions were compared to all other sunitinib sum Ctrough levels where after no dose reduction was necessary.
Results: A total of 57 patients were included in this study, of whom 39 with RCC and 18 with GIST. The median age was 60 years (range 24-80) and 73.7% of patients were male. Continuous dosing was mostly used. A total of 195 sunitinib samples were available, with a median of 3 samples per patient (range 1-19). The median duration of sunitinib treatment was 32 weeks (range 2-264) for patients with RCC and 65.5 weeks (range 7-570) for patients with GIST. The dose normalized median sunitinib sum Ctrough in patients with RCC and GIST was 50.6 ng/ml and 44.7 ng/ml, respectively. In 28 patients (49.1%) with clinically relevant toxicity, sunitinib sum Ctrough until dose reduction was significantly higher compared to patients without clinically relevant toxicity (median 59.1 ng/ml versus 46.1 ng/ml; P=0.001). The sunitinib sum Ctrough¬ after dose reduction was comparable to that of patients without clinically relevant toxicity (42.7 ng/ml; P=0.581). The median time on sunitinib until toxicity was 9.5 weeks (range 2-189). The median sum Ctrough level measured directly before dose reduction (n=36, 18.5%) was higher compared to other sunitinib samples (65.5 ng/ml versus 42.0 ng/ml; P<0.001).
Conclusions: This study demonstrated in a real-life patient cohort that sunitinib exposure is associated with the occurrence of clinically relevant toxicity. Furthermore, after dose reduction, sunitinib exposure is comparable to patients without clinically relevant toxicity. Surprisingly, toxicity seems to occur at a lower exposure compared to previously described in literature.

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Clinical pharmacoloGy of platinUm-based hyperThermic intraperitoneal chemotherapy: exploration of the impact of flushing on tumOur, systemic and personnel eXposure (GUTOX)

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Background
Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is standard of care for the treatment of patients with peritoneal carcinomatosis. Although the surgical procedure is standardised, large variety exists in HIPEC procedures. One of these variations consists of the use or non-use of additional flushing with crystalloids after removing the peritoneal chemotherapy at the end of HIPEC. The GUTOX study was performed to investigate the effect of flushing after HIPEC on platinum concentration in peritoneal tissue, systemic exposure and platinum contamination in drainage liquid.

Materials & methods
Twenty patients with peritoneal carcinomatosis, due to colorectal cancers, who were planned for HIPEC treatment with oxaliplatin as part of routine clinical care were included in the GUTOX study. The first ten patients were treated with CRS-HIPEC including flushing afterwards followed by ten patients who were treated with CRS-HIPEC without flushing afterwards. In both groups peritoneal tissue was harvested at the end of the 30-minute oxaliplatin perfusion. In the group with flushing a second peritoneal tissue sample was taken immediately after flushing with crystalloids. In addition to these peritoneal tissue samples, blood, peritoneal fluid and drainage liquid was taken at predefined time points to examine systemic exposure, degradation of platinum concentration in perfusate and drainage liquid. Platinum concentrations were analysed using flameless atomic absorption spectroscopy (AAS). A paired samples t-test on log-transformed data was performed to compare the platinum concentration in peritoneal tissue samples before and after flushing. Independent t-tests on log-transformed data were performed to compare systemic exposure and platinum contamination in drainage liquid between the two groups.

Results
No difference was found in platinum concentration in peritoneal tissue before and after flushing. Platinum tissue showed a remarkable broad range of concentrations (64 - 1640 ng/mg dry tissue). The non-flushing group showed higher systemic total platinum exposure compared to the flushing group (geometric mean [range] 116.4 [79.5-168.4] µg/ml*h vs. 90.4 [62.3 – 105.8] µg/ml*h, respectively; P=0.02). This was also the case for systemic ultrafiltrate platinum, although not statistical significant (geometric mean [range] 18.1 [10.8 – 28.0] µg/ml*h vs. 14.8 [10.5 – 20.2] µg/ml*h; P=0.14).This effect was caused by a difference in absorption between both groups, reflected by a difference in both Cmax for total platinum (geometric mean [range] 8.0 [5.5 – 11.5] µg/ml vs 6.3 [5.0 – 8.5] µg/ml, respectively; P= 0.02) and Cmax for ultrafiltrate platinum (geometric mean [range] 5.9 [3.4 – 8.7] µg/ml vs. 4.6 [3.5 – 5.7] µg/ml, respectively; P=0.04). Platinum concentration in peritoneal fluid decreased by approximately 30% during the 30-minute HIPEC procedure. Although the total amount of platinum cleared via drainage liquid was higher in the non-flushing group (geometric mean [range] 6.3 [3.0 – 11.8] mg vs. 4.5 [2.6 – 7.7] mg; P=0.05), there was no difference in platinum concentration in drainage liquid between patients of both groups (geometric mean [range] 7.7 [3.8 – 14.6] µg/ml vs. 7.6 [2.8 – 21.1] µg/ml; P=0.95).

Conclusion

There is no effect of flushing after HIPEC on platinum concentration in peritoneal tissue. Furthermore, platinum concentration in drainage liquid is not affected by the flushing. Therefore, HIPEC without flushing afterwards can be performed to simplify the procedure.

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Biomarker-based dose individualisation of axitinib in metastatic renal cell carcinoma (mRCC): A simulation framework

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Objectives: The optimization of dose and schedule of tyrosine kinase inhibitors (TKIs) has increasingly gained attention as a means to improve clinical outcome [1]. It is generally accepted that increased drug exposure correlates with prolonged overall survival. However, the occurrence of toxicity restrains the possibility for dose escalation. Dose individualisation based on either drug plasma levels (e.g. therapeutic drug monitoring (TDM)), relative change in diastolic blood pressure (ΔdBP) or serum biomarkers (i.e. soluble vascular endothelial growth factor receptor (ΔsVEGFR)-3), has been brought forward in order to balance treatment benefit against adversity [2-5]. Additionally, the intermittent administration of high-dose TKIs might ultimately result in higher plasma concentrations, giving rise to enhanced efficacy [6]. Exploration of each method by means of model-based simulations represents a convenient and low-cost method to visualize the effect of each strategy and might support the development of hypothesis to be tested in clinical trials [5].

Methods: A previously developed pharmacodynamic framework describing the relations between axitinib exposure, renal cell carcinoma tumor size, dBP, sVEGFR-3 and OS [4] was translated to mrgsolve [7]. The framework was further extended by a population pharmacokinetic (popPK) model [8]. Initial simulations were performed with fixed dosing at 5 mg twice per day (b.i.d.) [9] and the correlation between axitinib trough concentration (Ctrough) and area under the curve (AUC) was established. Once weekly (QW), and once every 2 week (Q2W) administration of high-dose axitinib was compared to standard continuous dosing for their effect on dBP and OS. Lastly, dose adjustments based on TDM, changes in dBP and sVEGFR-3 were simulated with a discrete number of possible axitinib doses (0, 2, 5, 7 and 10 b.i.d.). Threshold values for each biomarker-based dose-individualisation method (Ctrough, ΔdBP and ΔsVEGFR-3) were based on the minimal value that achieved a 4% absolute increase in OS after 100 weeks of axitinib therapy. Accuracy of each biomarker was verified by re-simulation of OS using the fixed threshold values, while resampling the population distributions. Here Accuracy = [No. simulations survival > 4% / Total no. of simulations x 100%].

Results: Pearson's correlation coefficient was 0.911 ($p < 0.001$, n=1000) for Ctrough and AUC. High-dose axitinib at 70 mg QW, or 140 mg Q2W was predicted to decrease OS at 100 weeks compared to fixed dosing at 5 mg b.i.d. (58.1% (95%CI 54.7-61.6) and 47.6% (95%CI 42.6-53.3) versus 64.6%, respectively) (n=1000). Thresholds for dose titration were fixed to Ctrough < 5 ng/ml, ΔdBP < 0.20 and ΔsVEGFR-3 > 0.45. Accuracy of each biomarker was simulated by resampling the population-and model-based distributions (no. simulations = 50): Ctrough = 32%, dBP = 22%, sVEGFR-3 = 40%.

Conclusions:
Ctrough appears to be a reasonable, and more convenient, drug plasma concentration alternative to AUC. Simulations with current models suggest that QW, or Q2W, high-dose axitinib at the cumulative weekly dose might decrease OS as compared to daily dosing, possibly due to the short-half life of axitinib. sVEGFR-3 appears to be the most accurate biomarker to guide dose-individualisation, which was expected given its high correlation to OS and relatively low intra-occasional variability.

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Quantification of the tyrosine kinase inhibitor erlotinib in human scalp hair by liquid chromatography-tandem mass spectrometry: Pitfalls for clinical application.

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Background:
An LC-MS/MS method was developed and validated to quantify the tyrosine kinase inhibitor erlotinib in human scalp hair, as alternative matrix to monitor long-term erlotinib exposure.

Materials and methods:
Hair samples from 10 lung cancer patients were measured and correlated with plasma concentrations. Hair segments of 1 ± 0.1 cm each were pulverized and for at least 18 h incubated in methanol at ambient temperature. A liquid-liquid extraction purified the extracts and they were analyzed with LC-MS/MS, using erlotinib-d6 as internal standard.

Results:
The procedure method was validated for selectivity, sensitivity, precision, lower limit of detection, linearity and accuracy. The within and between run precisions including the lower limit of quantification did not exceed 12.5%, while the accuracy ranged from 103 to 106%. A weak correlation between hair and plasma concentration was found (R2 = 0.48). Furthermore, a large inter-individual variability was noted in the disposition of both plasma and hair samples. The highest hair concentrations were observed in black hair compared with other (grey and brown) hair colors. Generally, a linear reduction in hair concentration was found from proximal to distal hair segments. Additional in vitro experiments suggest an accelerated degradation of erlotinib in hair by artificial UV light and also wash-out by shampoo mixtures pretreatment compared with control samples.

Conclusions:
In conclusion, a reliable and robust LC-MS/MS method was developed to quantify erlotinib in hair. However, clinical and in vitro evaluations showed that the method is not suitable for monitoring long-term erlotinib exposure. The pitfalls of this application outweigh the current benefits.