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Investigation of causes of drug-induced pyrexia in patients with BRAF V600E/K metastatic melanoma treated with dabrafenib and trametinib

Background. The combination of a BRAF inhibitor dabrafenib and a MEK inhibitor trametinib (CombiDT) has improved survival outcomes compared with chemotherapy or dabrafenib in advanced BRAF V600E/K melanoma. However, the use of CombiDT has a high incidence of pyrexia (50-70%). Understanding the etiology of pyrexia would maximise the proven benefit of CombiDT therapy. Our aim was to investigate if and to what extent the pharmacokinetics (PK) of dabrafenib and trametinib contribute to pyrexia, and to investigate an association between inflammatory cytokines and pyrexia.

Materials & Methods. The study included 37 patients with Stage 3 BRAF V600E/K melanoma treated with CombiDT, recruited onto Neo Adjuvant Combi Trial (protocol ID: 200332) between August 2014 to June 2017. Blood samples were collected during the 12 weeks of neo-adjuvant treatment. Plasma concentrations of drugs and metabolites were determined using validated LCMS assays. Population PK model was applied to dabrafenib and trametinib data using NONMEM. A panel of inflammatory cytokines was also measured in patients.

Results. Dabrafenib concentrations ranged from 4.0-4628 ng/ml and trametinib from 1.0-45 ng/ml in 139 (dabrafenib) and 162 (trametinib) post-treatment samples from 34 patients. N-desmethyl-dabrafenib was the most prevalent metabolite, followed by carboxy- and then hydroxy-dabrafenib. A 2-compartment model with first-order absorption provided the best fit to the dabrafenib and trametinib data. Association between pyrexia and higher AUC or Cmin for the drugs or higher peak metabolite ratio could not be observed from our data. Increase in Interleukin (IL)-1B and IL-6 at early days of treatment (EDT: day 4-7) from baseline were 1.9-fold (p=0.029) and 2.5-fold (p=0.028) higher respectively in pyrexia group compared to no pyrexia group.

Conclusions. In our study, potential causes of drug-induced pyrexia were investigated. However, apparent relationship between exposure to drugs or metabolites, and pyrexia was not observed. A greater increase in levels of IL-1B and IL-6 were observed in patients with pyrexia. A high proportion of patients with pyrexia (71%) and only 12% (4 patients) without pyrexia/treatment interruptions were limitations to observing any further apparent relationships between the investigated factors and pyrexia.

The Relationship Between Busulphan AUC and the Incidence of Sinusoidal Obstruction Syndrome in Haematopoietic Stem Cell Transplants

Background

High dose intravenous busulphan (Bu) is an essential component of myeloablative regimens prior to haematopoietic stem cell transplantation (HSCT) and has a narrow therapeutic window. This is a challenge for accurate dosing because it is subject to significant inter- and intra-individual pharmacokinetic (PK) variability and excessive exposure is associated with sinusoidal obstruction syndrome (SOS). We investigated the factors underlying the PK variability of Bu in relation to the incidence of SOS.

Materials and Methods

Pharmacokinetic and transplant-relevant data were collected on 344 myeloablative conditioned transplants (264/80 allogeneic vs autologous) in 337 patients (204 adult and 133 paediatric) at 7 institutions across Australia between 2006-2017. Drugs used in addition to Bu included cyclophosphamide (n=123), melphalan (n=120), fludarabine (n=159) and thymoglobulin (n=97). Bu was dosed according to actual bodyweight (ABW) and adjusted-ideal bodyweight (AIBW) in overweight patients. Bu concentrations (n=3241) were used to develop a population PK model (NONMEM version 7.3). Weight with allometric scaling was incorporated as a covariate to account for the large variability in body size of the patients. A maturation function was used to describe the clearances of the youngest patients. Daily AUC was estimated as dose divided by individual clearance and cumulative AUC (cAUC, the sum of all AUCs for a patient in one myeloablative conditioning episode.) The association between SOS and relevant transplant related factors was assessed using Mann-Whitney tests, and uni- and multivariate Cox regression analyses between time to SOS and transplant related factors such as conditioning regimen, pre-transplant albumin, concomitant medications, ABW and AIBW, and type of transplant (allogeneic vs autologous). Diagnosis of SOS was made by clinicians using revised Seattle and Baltimore criteria following the HSCT.

Results

Median age was 30 years (40 days to 70 years) and SOS prophylaxis with ursodeoxycholic acid was administered to 71% of the patient cohort. A one-compartment model with proportional error on log-transformed concentration data provided the best fit to the 3,241 observations. Intra-occasion variability on CL and V further improved the model (dOFV -361). Clearance (12.9 L/h) and volume of distribution (48 L) were consistent with literature values.

Sixty-four patients were diagnosed with SOS (43 of 133 paediatric, and 21 of 204 adults). There was no difference in the cumulative AUC for patients with or without SOS, 77 mg/L.h (42-123 mg/L.h) and 76 mg/L.h (28-132 mg/L.h), respectively.

A univariate Cox proportional-hazards analysis revealed a decrease in hazard of SOS of 0.028 0.026, and 0.035 for every year increase of age (p= 1.8×10^{-5}) for every kg of AIBW (p= 8.7×10^{-8}) and for every g/L increase in pre-transplant albumin levels (p= 0.00068). Other factors such as cumulative AUC, or concomitant use of metronidazole or paracetamol were not associated. On multivariate analysis the only independent factor was higher AIBW (a decrease in hazard of 0.16 for every kg increase; p= 0.007).

Conclusion

Based on these findings, variation in Bu cAUC does not explain the incidence of SOS. Lower AIBW, which correlates with younger age, is significantly associated with SOS incidence.

A Randomized Bayesian Phase 1 Design Combining an MPS-1 Inhibitor with Paclitaxel: a Strategy to Improve Determination of The Incremental Toxicity of a Novel Compound over a Known Backbone Therapy

Background
Here we present a study combining BAY1217389 (BAY), a potent MPS-1 kinase inhibitor with a backbone chemotherapy paclitaxel. Since we expected overlapping toxicities we sought to improve determination of the maximal tolerated dose (MTD) using a randomized phase 1 design with Bayesian dose modeling. We hypothesized that this approach may determine the MTD of BAY more accurately by limiting the effect of variability of dose limiting toxicities (DLTs) related to paclitaxel.

Methods:
Patients (≥18 years) were randomized to receive oral BAY with intravenous paclitaxel (experimental arm) or paclitaxel monotherapy (standard arm) in cycle 1. Dose escalation was guided by Bayesian modeling targeting a DLT-rate in the experimental arm of 10% over DLT-rate in the standard arm. PK profiles were determined for both BAY and paclitaxel. Simulations were performed to estimate MTD for several scenarios.

Results
We were able to establish an MTD of 65 mg BAY using 50 patients in the dose-escalation part. As expected the main DLTs were hematologic toxicity. Grade ≥ 3 neutropenia was predominantly observed in the experimental arm and was related to higher BAY AUC_{0-12} on D8 (p<0.001) and not to paclitaxel AUC_{0-24} (p>0.1). To determine whether the randomization adds value to the study design we ran simulations comparing our randomized strategy using variable toxicity rate (5, 10, 20, 40%) for paclitaxel monotherapy with the 3+3 design. These data showed that the randomized design outperformed the 3+3 design. The 3+3 design underestimated the MTD as dose escalation was terminated more frequently at first dose for higher paclitaxel toxicity rate.

Conclusions
Randomized Bayesian phase 1 dose escalation design was feasible with BAY plus paclitaxel. A major advantage of this design is the precise determination of an exposure-toxicity relation for the experimental drug. Moreover, simulations support our hypothesis that the randomized design was able to determine the MTD accurately regardless of variable toxicity rate for paclitaxel. This approach may improve dose determination in phase I combination trials.

5

Influence of the proton pump inhibitor esomeprazole on the bioavailability of regorafenib

Background:
The multikinase inhibitor regorafenib is currently registered for the treatment of colorectal cancer (CRC), gastrointestinal stromal tumors (GIST), and hepatocellular carcinoma. Regorafenib exhibits a pH-dependent solubility, and therefore acid reducing drugs such as proton pump inhibitors (PPIs, e.g. esomeprazole) might reduce regorafenib absorption by increasing the stomach pH as was shown for many other kinase inhibitors. We performed a randomized, 3-phase, cross-over trial to compare the exposure of regorafenib alone to regorafenib with esomeprazole (concomitantly or 3 hours prior to regorafenib intake) in CRC and GIST patients.

Materials & Methods:
Patients were randomized into 2 sequence groups consisting of 3 phases: regorafenib intake alone, regorafenib with concomitant esomeprazole (for 5 days), and regorafenib 3 hours preceded by esomeprazole (for 5 days). Pharmacokinetic (PK) blood sampling was performed at the 21th, 49th and 77th day of the trial. All patients were treated with regorafenib 120 mg at steady-state. Primary endpoint was the relative difference (RD) in geometric means for regorafenib area under the curve for 24 hours (AUC0-24h). A linear mixed model was used to analyze log-transformed AUC0-24h. For multiple testing a Bonferroni correction was applied.

Results:
A total of 14 patients were evaluable for the primary endpoint. Exposure (AUC0-24h) to regorafenib alone was: 55.9 µg*h/mL (coefficient of variation (CV): 40.3%). For regorafenib with concomitant esomeprazole or with esomeprazole 3 hours prior AUC0-24h was: 53.7 µg*h/mL (CV: 33.5%) and 53.6 µg*h/mL (CV: 42.6%) respectively. No significant differences were identified when regorafenib alone was compared to regorafenib with concomitant esomeprazole (RD: -3.9%, 95% CI: -20.5-16.1%, p=1.0) or regorafenib with esomeprazole 3 hours prior (RD: -4.1%, 95% CI: -22.8-19.2%, p=1.0). Furthermore, no significant differences were observed in other PK parameters of regorafenib and its active metabolites M-2 and M-5 (i.e. Cmax, Tmax). Most common adverse events ≥ grade 2 were hypertension (71%), fatigue (43%) and hand foot skin reaction (36%).

Conclusions:
The use of esomeprazole concomitantly or 3 hours prior to regorafenib intake did not alter regorafenib pharmacokinetics. Our results indicate that PPIs like esomeprazole can be combined with regorafenib without the appearance of a significant drug interaction.

6

Influence of the number of tumor size measurements on model-derived tumor size metrics and estimated hazard of death

Objectives: The tumor size ratio (TSR), time-to-tumor growth (TTG) and natural tumor growth rate (KG) have frequently been suggested as predictors of overall survival (OS) in model-based analyses. However, it should be acknowledged that all available longitudinal tumor size measurements in a study are typically used to estimate these metrics for an individual patient. This study aims to investigate how the number of available tumor size measurements per patient may influence the accuracy of predicting the true tumor size metrics for an individual patient, which in turn could influence the metrics' value to at an early time point estimate the hazard (HZ) of death.

Methods: Tumor size data for 1000 subjects were simulated, using a simplified tumor growth inhibition model for bevacizumab plus chemotherapy in colorectal cancer (Claret et al.,2013), at baseline(w0), and at 6,12,18,24,36,48,60,72,84 and 96 weeks. Dropout from tumor measurements was forced at an observed increase from the tumor nadir of >20%. The OS was described by a Weibull function and a relationship to the tumor metric. For each individual, the 'true' TSR at week 6 (TSRw6), TTG, KG and corresponding HZ were derived from the simulated tumor size time-course. The accuracy was calculated as the percentage deviation from the 'true' value and the acceptable accuracy was set to 80-125% of the 'true' value.

Results: As expected, the accuracy of tumor metrics and estimated HZ was improved as the number of measurements increased. TSRw6: With only baseline and w6 measurements, the accuracy of the predicted TSRw6 and estimated HZ was within the acceptable range for 70% of the patient population. By adding a w12 measurement, most of the individuals (about 80%) had acceptable accuracy. The accuracy was little affected by adding later observations. TTG: The accuracy in TTG predictions and estimated HZ was in general low; the percentage of individuals with acceptable accuracy of TTG and estimated HZ was increased from 30% to 40% when increasing from 2 to 4 observations, while additional measurements only marginally affected the accuracy. KG: The percentage of individuals with acceptable KG accuracy was improved from 41% (2 observations) to 77% when all 11 observations were used and the accuracy of estimated HZ was improved from 54% to 62% of the population.

Conclusions: This simulation study demonstrates that TSRw6 is a more promising metric than TTG or KG for early prediction of treatment outcome for an individual patient since fewer measurements are needed for adequate estimation of the metric and for predicting OS. In addition to baseline and a w6 measurement, a w12 measurement appears beneficial for accurate estimation of an individual's TSRw6. TTG and KG showed overall a lower accuracy and required a longer follow-up (> 18 weeks) for improving the accuracy of the metrics and the estimated HZ of death. A joint (simultaneous) analysis of tumor size and OS showed only a small improvement of the accuracy of the estimated HZ compared to a sequential analysis.

7

A real-life study on the implementation and effectiveness of exemestane plus everolimus per hospital type in patients with advanced breast cancer.
A study of the Southeast Netherlands Breast Cancer Registry.

BACKGROUND: The aim of this study was to assess the implementation and effectiveness of exemestane plus everolimus treatment per hospital type in real-life, shortly after approval of everolimus.
MATERIAL AND METHODS: Advanced breast cancer patients treated with exemestane plus everolimus in 2012-2014 were included from the SOutheast Netherlands Advanced BREast cancer (SONABRE) Registry. Hospitals were classified as academic, teaching, or non-teaching. Progression-free survival (PFS) and a 12-week conditional PFS (post-hoc) were estimated by the Kaplan-Meier method. The multivariable Cox proportional hazards model was stratified by type of hospital and adjusted for patient, tumour and treatment characteristics.
RESULTS: We included 122 patients, comprising 48 patients treated in an academic (N=1), 56 in teaching (N=4), and 18 in non-teaching (N=2) hospitals. The median PFS was 6.3 months (95% Confidence Interval (CI) 4.0-8.6) overall, and 8.5 months (95% CI 7.7-9.3), 4.2 months (95% CI 2.0-6.3), and 5.5 months (95% CI 4.2-6.7) for the patients treated in academic, teaching and non-teaching hospitals, respectively. The adjusted Hazard Ratio (HR) for PFS-events was 1.5 (95% CI 1.0-2.2) and 1.0 (95% CI 0.5-1.9) respectively for patients treated at teaching and non-teaching hospitals versus the academic hospital. In contrast, the adjusted HR for 12-week conditional PFS-events was not different between hospital types. In the first 12-week treatment period, treatment was discontinued in 10% of patients treated in the academic versus 21% of the patients treated in non-academic hospitals.
CONCLUSION: In our real-life implementation-phase study, the median PFS was statistically borderline different between hospital types due to a difference in number of PFS-events in the first 12-week treatment period. This seemed to be the result of a different assessment approach. We recommend physicians to broadly share treatment protocols and treatment experience to improve the implementation of therapies.

A pharmacometric framework for dose individualisation of sunitinib in GIST

Objectives: Several dosing strategies have been proposed for sunitinib, based on either plasma drug concentration, adverse events or soluble biomarker measurements [1-3]. Therapeutic drug monitoring (TDM) of trough concentration has recently gained momentum as a method to guide dose decisions, but does not account for the large inter-individual variability in the susceptibility of efficacy and safety endpoints [4,5], i.e. in the concentration-response relationships. Moreover, TDM may not be feasible in each country or treatment center due to practical and economical constraints. Vascular endothelial growth factor receptor (sVEGFR)-3 or neutrophil counts and blood pressure, have been demonstrated to be stronger predictors of overall survival (OS) in gastrointestinal stromal tumour (GIST) and could therefore be used to guide dosing decisions [2,3]. We explored a model-based adaptive feedback approach to increase OS in sunitinib-treated GIST patients, wherein individual dose-adjustments depend on pharmacodynamic biomarkers, such as adverse events (blood pressure and neutrophil counts), or sVEGFR-3.

Methods: A previously developed pharmacometric framework was translated into the mrgsolve simulation package [2,3,6]. The final framework encapsulated the relationship between plasma exposure, adverse events (hand-foot syndrome (HFS), fatigue, hypertension and neutrophil counts), sVEGFR-3 and OS. Dose-limiting toxicities were defined as ≥Grade 2 for HFS and thrombocytopenia and ≥Grade 3 for the remaining adverse events, according to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE). Baseline schedules consisted of sunitinib 37.5 mg once daily, with possible adjustments to alternative discrete doses (0 to 75 mg, by 12.5 mg increments). Sunitinib concentration (TDM), adverse event and sVEGFR-3-based dose adjustments were simulated according to a proposed schedule by Lankheet et al. Herein, biomarker levels were measured at week 2, 4 and 8, and if these fell outside of a predefined window, sunitinib dose was increased by 12.5 mg. [4]. Lastly, maximum a-posteriori estimations were performed for various sampling schedules in order to explore the advantage of a model-based dosing algorithm.

Results: sVEGFR-3-based dose adaptations increased median OS compared to fixed dosing (25.5 versus 21.7; HR 0.90) and TDM (25.5 versus 21.2 months; HR 0.77). Similarly, AE-based dose adaptations increased median OS as compared to a fixed dose schedule (24.1 vs. 20.0 months; hazard ratio [HR] 0.90) and TDM-based dose adjustments (24.1 vs. 19.7 months; HR 0.81), without markedly raising the risk of intolerable toxicities. Bayesian estimations of blood pressure, sVEGFR-3 and neutrophils were accurate (80-125% of true value) for 28.5%, 64.6% and 73.5% of patients after three observations (routine sample at day 0, 15 and 29) and 35.1%, 76% and 85.6 % of patients after daily observations (day 0-29), respectively.

Conclusions: Adverse event and sVEGFR-3-based dose adaptations may provide viable guidance for dose individualisation of sunitinib in patients with GIST, and is predicted to increase OS. Neutrophil-based dose adjustments are favored, as these are already measured in routine clinical practice and will therefore not necessitate additional hospital visits or expenses. This is the first framework-based Bayesian decision support tool to include not only drug concentration, but also models for biomarkers, adverse events and OS.

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Impact of curcumin with or without piperine on the pharmacokinetics of tamoxifen

Background:
Tamoxifen is extensively used as endocrine therapy for breast cancer. It is a prodrug that is primarily metabolized in two steps by CYP3A4 and CYP2D6, particular into the pharmacologically active metabolite endoxifen. The herb curcumin is widely used among cancer patients, because of its presumed anti-tumor effects. However curcumin may increase endoxifen exposure by affecting phase I and II drug metabolism. Therefore, we performed a randomized cross-over study to compare endoxifen and tamoxifen exposure in breast cancer patients with or without curcumin, and with the addition of the bio-enhancer piperine.

Patients and methods :
Pharmacokinetic sampling was performed in 16 patients on day 28, 56 and 84 of the study. in the 28 days prior to pharmacokinetic sampling tamoxifen (20-30mg q.d.) was either given alone, or combined with curcumin (1,200mg t.i.d.) with or without piperine (10mg t.i.d.) in this order or vice versa. Genotyping was performed to determine CYP2D6 and CYP3A4 phenotypes. The primary endpoint of this study was the difference in geometric means for the area under the curve (AUC) of endoxifen. A linear mixed model was used to analyze log-transformed area under the curve (AUC). For multiple testing a Bonferroni correction was applied.

Results:
The endoxifen AUC0-24h decreased with 7.7% (95%CI: -15.4 to 0.7%; P=0.07) with curcumin and 12.4% (95%CI: -21.9 to -1.9%; P=0.02) with curcumin and piperine, compared to tamoxifen alone. Furthermore the tamoxifen AUC0-24h showed a decrease of 8.0% (95%CI: -14.1% to –1.4%, P=0.02) with curcumin and 12.8% (95%CI: -19.2% to -5.9%, P<0.01) with curcumin and piperine. Other pharmacokinetic parameters showed similar results. For patients with an extensive metabolism phenotype, effects of curcumin with piperine on endoxifen and tamoxifen exposure were more pronounced than for intermediate metabolizers.

Conclusions:
In contrast to our hypothesis, the exposure to tamoxifen and endoxifen was significantly decreased by concomitant use of curcumin (with and without piperine). Although limited effects were observed in most patients, co-treatment with curcumin could lower endoxifen concentrations below the threshold for efficacy (potentially 20-40% of the patients), especially in patients with an extensive metabolism phenotype.

A Pharmacokinetic-Pharmacodynamic binding model of Bevacizumab to VEGF as a tool to optimize treatment

Background

Most of the targeted treatments have been associated with specific biomarkers, predictive of the response. Although antiangiogenic agent bevacizumab is widely used, there are still no available biomarkers used routinely in clinical practice. In addition, monoclonal antibodies exhibit more complex pharmacokinetic (PK) and pharmacodynamic (PD) characteristics than small molecules. Their disposition is often influenced by their binding affinity to their molecular targets. Given the need of developing more individualized treatment approaches and the high cost of bevacizumab, the aim of the present study was to develop a PK-PD model including binding properties between bevacizumab and his molecular target VEGF in patients with metastatic colorectal cancer (mCRC). The effects of patient's characteristics (age, sex, genetics) on the model were also studied.

Methods

46 patients with mCRC treated with bevacizumab in combination with chemotherapy (fluoropyrimidines and oxaliplatin or irinotecan) as first-line treatment were enrolled. Trough and peak levels of total bevacizumab and free VEGF were measured in serum during several cycles of treatment. Moreover, the effect of sex, age and selected VEGFA (rs2010963, 1570360, rs699947) single nucleotide polymorphisms (SNPs) was investigated. Levels of total bevacizumab were measured using a previously published enzyme-linked immunosorbent assay (ELISA), where the detection limit was 0.033 mg/L and the range of linearity was between 5 and 75 mg/L with precision 5.6 %. A commercially available ELISA kit measured levels of free VEGF for VEGF (Quantikine® human VEGF, R&D Systems® Europe). The detection limit of the assay was 9 ng/L, and the precision was 6.7%. SNPs were detected using PCR-based Sanger sequencing. PCR amplification was carried out according to the KAPA2G Fast HotStart protocol (KAPABIOSYSTEMS, MA, USA). Regarding the statistical methods, the Spearman's rank correlation coefficient was used to study the correlation between VEGF and Bevacizumab. For the multiple analysis, we used linear regression with residual analysis and considering multicollinearity while the effects are reported with 95% confidence intervals. The ethical committee of University Hospital of Patras approved this study.

Results

Of the 46 patients enrolled 61% were males and 39% females, the mean age of the study population was 64.5 years (31-86). In total 171 samples for VEGF and 157 for Bevacizumab levels were collected and analyzed. Very strong negative correlation between Bevacizumab and VEGF levels (Coef. = -0.625, p<0.000001) was noted; this correlation was not associated with age or sex. Interestingly, rs699947 plays an important role in the model (p=0.0002, 95% CI 32.5-58.1) and as VEGF levels were found to be significantly lower in homozygous patients (p<0.0001, 95% CI 25.2 - 53.8).

Conclusion

In conclusion, we found a very strong negative correlation between bevacizumab and VEGF levels. Genetic factors significantly influence the model and significantly lower VEGF levels were measured in patients homozygous for rs699947. These results may explain the favorable clinical results reported previously by

other studies in this sub-group of patients. This model might enable us to distinguish patients, who may benefit more and in a long-term and also can be used to improve dosing of bevacizumab in order to achieve better results.

Analysis of the involvement of cytochrome P450 isoenzymes in the metabolism of antineoplastic medicines

Background
At present, the number of patients with oncological diseases is increasing. Combination therapy (surgical, radiation, drug, photodynamic, biotherapy) allows to achieve maximum therapeutic effect on the cancer. Drug therapy also is a complex. Side effects of antineoplastics are suppressed not only by correction of doses, but also by the administration of other drugs. Such combinations are often the causes of medicine interactions. If pharmacodynamic interactions can be avoided and prevented in advance (mechanism of action is known), it's sometimes impossible to predict pharmacokinetic interactions (because of their insufficient study). Knowledge of substrates, inhibitors and inducers of cytochrome P450 (CYP450) enzymes helps in predicting interactions.

Materials & Methods
In work, analytical, statistical, comparative methods were used. The materials were scientific research in vitro and in vivo, concerning antineoplastics contained in databases: Transformer database, Academia.edu, PubMed, PubChem, DrugBank.

Results
Analysis of metabolism of 200 antineoplastic medicines (by ATC-classification) established the role of CYP450 in the conversion of these drugs. So 85 (42.5%) of medicines are metabolized by CYP450. Metabolism 85.4% of medicines protein kinase inhibitors, 78.6% of plant alkaloids and 42.2% of other antineoplastic agents are carried out through CYP450. Procarbazine is completely metabolized by CYP1A2, CYP1B1. Among alkylating agents, involvement in the metabolism via CYP450 was 30.8% drugs, cytotoxic antibiotics - 31.3%, platinum compounds - 40.0%, antimetabolites - 16.7%, monoclonal antibodies - 3.7%. Medicines from the group of photodynamic/radiation therapy aren't metabolized with CYP450. The main isoenzyme of CYP450 involved in metabolism of cyclophosphamide, ifosfamide, trophosphamide, thiotepa is 3A4, carmustine and dacarbazine - 1A2, lomustine - 2D6. Cyclophosphamide, ifosfamide, mitobronitol, temozolamide, dicarbazine have inducing effect on CYP450, thiosulphane, thiotepa, lomustine - inhibitory effect. Three antimetabolites are metabolized by CYP450: cytarabine - mainly 3A4, tegafur and fluorouracil - 2A6. Fluorouracil and capecitabine inhibit 2C9. Isoenzyme 3A4 is main in the metabolism of plant alkaloids (except for teniposide – 2C19, paclitaxel – 2C8). These alkaloids inhibit activity of 3A4. Vintafolide, demecolcine, paclitaxel poliglumex isn't metabolized via P450. Main isoenzymes involved in the metabolism of ixabepilone, doxorubicin and daunorubicin are 3A4, mitoxantrone - 2E1, idarubicin - 2C9, 2D6. Cisplatin and oxaliplatin are substrates 2E1. The main metabolite of brentuximab vedotin (after recycling or elimination of the amino component) is substrate of CYP3A4, CYP2D6. The main isoenzyme responsible for the metabolism of kinase inhibitors is CYP3A4. In metabolism of these drugs are involved subfamily CYP2C. Other antineoplastics are metabolized mainly CYP3A4. Bortezomib, anagrelide, ixazomib - substrates 1A2. Celecoxib and vismodegib are metabolized by 2C9. The inhibitory and inducing effect of these drugs on enzymes has insufficient evidence. Thus, most antineoplastics are metabolized via CYP3A4. This should be taken into account when co-prescribing other drugs to avoid competitive pharmacokinetic interaction.

Conclusions
Information on the metabolism of 200 antineoplastic drugs is systematized, 42.5% of which are metabolized via CYP450 (mainly CYP3A4). However, in the metabolism of medicines are involved CYP2C enzymes. Protein kinase inhibitors and plant alkaloids are predominantly metabolized by several CYP450 enzymes (>70%). Knowledge of the major and minor enzymes allows predicting drug interactions.

Correlation between nivolumab exposure and treatment outcome in NSCLC

Background: Treatment with anti-PD-1 therapy is subject to large inter-individual variation in clinical outcome. This may be influenced partly by differences in nivolumab exposure between patients. The objective of the current analysis was to investigate whether an exposure-response relationship exists for nivolumab-treated NSCLC patients.

Materials & Methods: 84 patients started nivolumab treatment between May 5th 2016 and August 1st 2017 and were included for prospective collection of serum samples prior to each nivolumab cycle. Clinical data were collected until November 1st 2017. Patients were classified according to best objective response (BOR) according to RECIST v1.1 and the occurrence of grade ≥3 toxicities according to CTCAE v4.03. Geometric mean nivolumab trough concentrations after 2, 4, and 10 weeks of treatment were compared using ANOVA with respect to BOR and t-test with respect to toxicity in patients without dose delays until that particular time point.

Results: 76 patients were evaluable for analysis; 4 patients had no follow-up tumor evaluation, and 4 patients had no follow-up blood sample. At each time point, partial responders (PR; n = 15) had higher geometric mean trough concentrations when compared to patients with progression (PD; n = 33): at 2 weeks : 27.4 µg/mL (95% CI: 22.3 – 33.6 µg/mL) vs. 18.7 µg/mL (95% CI: 16.7 – 20.9 µg/mL; p = 0.001; 47% higher), at 4 weeks: 46.2 µg/mL (95% CI: 37.4 – 57.0 µg/mL) vs. 30.2 µg/mL (95% CI: 25.0 – 36.4 µg/mL; p = 0.008; 53% higher), at 10 weeks: 79.4 µg/mL (95% CI: 60.7 – 103.8 µg/mL) vs. 45.8 µg/mL (95% CI: 35.6 – 58.9 µg/mL; p = 0.002; 73% higher). Moreover, PR patients had higher trough concentrations when compared to patients with stable disease (SD; n = 28) at week 2 (p = 0.034) and at week 4 (p = 0.047). Exposure was not significantly related to the occurrence of grade ≥3 toxicity (n = 15) at any time point.

Conclusions: This analysis shows that NSCLC patients with an objective response to nivolumab have significantly higher nivolumab exposure than patients with early progressive disease, indicating an exposure-response relationship. Further clinical research is needed to explain and quantify this relation. If confirmed, more rational and individualized dosing-strategies can improve patient outcome.

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Therapeutic drug monitoring as a tool to reduce the occurrence of paclitaxel-associated peripheral neuropathy in patients with advanced NSCLC

Background: Peripheral neuropathy (PN) is a cumulative, dose-limiting toxicity of paclitaxel (PTX). More than 20% of patients treated with PTX doses >175 mg/m2, 3-weekly, experience clinically relevant PN [1], common toxicity criteria (CTC) [2] grades ≥2. PTX exposure, time of plasma concentration above a threshold (typically 0.05 µM, TC>0.05µM), has been shown to correlate with PN [3]. In the CEPAC-TDM study, pharmacokinetic/pharmacodynamic (PK/PD)-guided dosing significantly reduced neuropathy grades ≥2 compared to the standard BSA-guided dosing in NSCLC patients [4]. The above analysis [4] did not integrate times of occurrence of neuropathy, hence the impact of time-dependent processes e.g. changing drug exposure are neglected in comparing the risks of neuropathy with the two dosing strategies, potentially biasing the findings. In this work, parametric time-to-event (TTE) analysis, based on a published model [5], accounting for the time of occurrence of PN, was applied to quantify the risk of incidence of PN in PK/PD- and BSA-guided dosing to recommend dosing strategies that reduce the risk of PN.

Materials and methods: Patients from the CEPAC-TDM study who received PTX plus either cis- or carboplatin, 3-weekly, for ≤6 cycles, were included. PTX dosing was BSA-guided (n=182) or PK/PD-guided (n=183). PN symptoms, severity, start and end dates were recorded and classified using the CTC (V. 4.0) [2]. The impact of dosing strategy on the risk of incidence (1st occurrence) of PN grades ≥2 (PN2+) was evaluated using a published TTE model [5]. Using the TTE covariate model (including impact of dosing strategy on the risk of PN2+), 1000 trials were simulated based on the CEPAC-TDM data. The proportion of incident PN2+ was computed per trial and subsequently, risk ratios and Numbers Needed to Treat (NNT) statistics derived to compare risk of PN2+ between PK/PD- and BSA-guided dosing. The dataset was formatted in R and TTE analysis was performed in NONMEM 7.4.

Results: Overall, 105 incident PN2+ (28.8%) were reported, BSA-guided dosing arm (n=68, 37.4%) and the PK/PD-guided dosing arm (n=37, 20.2%). The estimated risk of PN2+ reduced by 50% with PK/PD-guided dosing. The percentage of patients predicted to experience PN2+ across the entire time on treatment was 17.5% and 28.9% for PK/PD- and BSA-guided dosing, respectively. This represented a PN2+ risk reduction (95% CI) of 39% (18%, 58%) with PK/PD-guided dosing. The NNT (95% CI) was 9 (6, 20) for PK/PD-guided compared to BSA-guided dosing i.e. 9 patients need to be treated following PK/PD-guided rather than BSA-guided dosing to prevent 1 patient from experiencing PN2+.

Conclusions: We quantified the reduction in risk of PN2+ associated with PK/PD-guided dosing of PTX, accounting for the time of occurrence of PN2+. Given NSCLC patients on PTX chemotherapy have advanced disease, with poor prognosis and there is currently no effective treatment of PN, PK/PD-guided dosing offers a strategy to reduce this debilitating toxicity, and improve patient quality of life. The parametric TTE model will be extended to account for the impact of PTX exposure and patient characteristics on PN2+ to further support dosing strategies to reduce the burden of PN2+.

Effects of Prednisone on Docetaxel Pharmacokinetics in Men with Metastatic Prostate Cancer: A Randomized Drug-drug Interaction Study

Background: Docetaxel has been approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in combination with prednisone. In hormone-sensitive (mHSPC) setting it is currently unclear whether docetaxel chemotherapy should be administered with or without prednisone. The role of corticosteroids in metastatic prostate cancer is controversial; they may have a favorable palliative effect, but prolonged use may lead to the development of severe toxicities. Furthermore, prednisone is known to induce the cytochrome P450 iso-enzyme CYP3A4, which is the main metabolizing enzyme of docetaxel, resulting in a possible drug-drug interaction (DDI). Therefore, we investigated the pharmacological aspects of the addition of prednisone to docetaxel chemotherapy in men with metastatic prostate cancer.

Methods: We conducted a prospective randomized pharmacokinetic (PK) cross-over study in metastatic prostate cancer patients (both mHSPC as mCRPC). Patients scheduled to receive at least 6 cycles of docetaxel (75 mg/m2) and who lent written informed consent, were randomized to receive either the first 3 cycles, or the last 3 consecutive cycles with prednisone (2dd 5mg). Pharmacokinetic blood sampling was performed during cycle 3 and cycle 6. Primary endpoint was the difference in docetaxel exposure, calculated as area under the curve (AUC0-inf), with concomitant prednisone, compared to exposure of docetaxel monotherapy and analyzed by means of a linear mixed model analysis on log-transformed data.

Results: Eighteen patients were evaluable for the primary endpoint. Docetaxel exposure with concomitant prednisone (geomean AUC0-inf 2784 ng*h/mL, 95% CI 2436-3183 ng*h/mL) was similar (1.8%; 95% CI -9.9% till 15.2%, p=0.75) as compared to docetaxel monotherapy (geomean AUC0-inf 2647 ng*h/mL, 95% CI 2377-2949 ng*h/mL). Exploratory analysis showed no toxicity differences between docetaxel monotherapy and docetaxel cycles with prednisone.

Conclusion: No significant difference in docetaxel concentrations was observed. In addition, we found similar toxicity profiles in absence or presence of prednisone. Therefore, from a pharmacokinetic point of view, docetaxel may be administrated without prednisone.

A new method for the determination of total and released docetaxel from docetaxel-entrapped core-crosslinked polymeric micelles (CriPec®) by LC-MS/MS and its clinical application in plasma and tissues in patients with various tumours

Background: CriPec® docetaxel is a novel formulation of docetaxel – covalently conjugated via a linker agent in a stabilized, 65 nm sized CriPec® nanoparticle. Docetaxel is released from CriPec® nanoparticles as a result of chemical hydrolysis of the ester linker, which is occurring at physiological conditions and minimized at pH 5.0. Application of CriPec® docetaxel leads ideally via more selective targeting to higher intratumoural drug concentrations and lower drug levels in healthy tissue compared to the conventional drug.

Materials & Methods: Total docetaxel was determined by incubation of human plasma with 0.5 M ammonium acetate buffer pH 7.4 for 3-days at 37 °C. Hereafter, a liquid-liquid extraction with 1-chlorobutane was performed using paclitaxel as internal standard. Chromatographic separations were performed on an Atlantis® T3 3 μm, 2.1 mm x 50 mm column (concentration >2,000 ng/mL) and on an Acquity UPLC® HSS T3 1.8 μm, 2.1 mm x 50 mm column (concentrations <2,000 ng/mL). Released docetaxel from CriPec® docetaxel nanoparticles was determined in human plasma stabilized with 5 M ammonium acetate, pH 5.0. Hereafter, a liquid-liquid extraction with 1-chlorobutane was performed using docetaxel-d5 in acetonitrile as internal standard. Released docetaxel and its internal standard were eluted.

Results: A sensitive, high-performance liquid chromatographic method was developed and validated, for determination of docetaxel from docetaxel-entrapped core-crosslinked polymeric micelles (CriPec®) in human potassium EDTA plasma and released docetaxel in order to discriminate the pharmacokinetic profile of total drug in plasma and tissues in relation to released drug. The validated ranges for total docetaxel were 2,000–100,000 ng/mL for the high concentrations, 2–500 ng/mL for the low concentrations and 0.250–100 ng/mL for released docetaxel.

Conclusion: This method was validated, in according to the FDA guidelines for bioanalytical method validation, and complies with the following validation parameters: linearity, precision, accuracy, specificity, stability and robustness. This newly developed assay met the required standards for validation and was applied successfully to support pharmacokinetic analysis in both serum and tissue in cancer patients treated with Cripec® docetaxel.

Keywords: LC-MS/MS; docetaxel; docetaxel-entrapped core-crosslinked polymeric micelles (CriPec®); nanomedicine; validation

Individualized pemetrexed dosing in patients with non-small cell lung cancer or mesothelioma based on renal function to improve treatment response.

Introduction

For the treatment of advanced non-small cell lung carcinoma (NSCLC) and mesotheloama the multi-targeted folate antagonist pemetrexed is indicated. Like many drugs the dosing of pemetrexed requires balancing the risks of sub-therapy and toxicity. In patients with a creatinine clearence <45 ml/min the use of pemetrexed is currently contraindicated. Pemetrexed is dosed based on body surface area while renal function is not taken into account for despite the fact that the systematic exposure of pemetrexed is exclusively determined by the dose and renal function. This results in 3 major problems.1) In patients with renal dysfunction, BSA-based dosing may lead to haematological toxicity because the clearance of pemetrexed is decreased. 2) Patients have to discontinue treatment due to the declining renal function, thus are exposed to a suboptimal treatment. 3) In patients with adequate renal function (GFR >45 ml/min) treatment may be improved by individualized dosing based on renal function. We aim to address these problems.

Aim: The overall objective of this study is to develop a safe and effective individualized dosing regimen for pemetrexed.

Methods:

This study will consist of three sub studies. IMPROVE-I is a single arm phase II pharmacokinetic safety study using a Simon two stage design to examine the feasibility of renal function-based dosing of pemetrexed in patients with renal impairment. IMPROVE-II is an open label, double arm, randomized study to compare renal function-based dosing of pemetrexed versus BSA-based dosing on attainment of therapeutic exposure. IMPROVE-III is an explorative microdosing study to assess the extrapolability of microdose pharmacokinetics to the pharmacokinetics of a therapeutic dose.

Pharmacokinetically-guided dosing of pemetrexed in a patient with renal impairment and a patient requiring hemodialysis.

Introduction: Pemetrexed is indicated for the treatment of non-small cell lung cancer and mesothelioma. Renal function is the sole determinant for systemic exposure, but dosing is based on body surface area (BSA) and does not take renal function into account. There is a well-established relationship between exposure, response and toxicity (neutropenia). In patients with renal dysfunction, BSA-based dosing may lead to haematological toxicity, therefore renal impairment is currently a contraindication for pemetrexed. Renal impairment is highly prevalent in patients with lung cancer. While these patients may be withheld effective treatment or treated with a potentially toxic dose, a safe dosing strategy taking renal function into account is needed. As a 'proof-a-concept' two cases, of a patient with moderate impairment and one patient requiring haemodialysis, are presented in which pharmacokinetically-guided dosing resulted in a tolerable treatment.

Method: The target exposure was an area under the concentration-time curve (AUC) of 123-205mg*h/L, a proven safe and effective target (systemic exposure in patients with adequate renal function treated with a pemetrexed dose of 500mg/m2). We measured plasma concentrations with a validated UPLC-UV method and estimated the individual AUC with Bayesian estimation, using a validated population pharmacokinetic model. Dose adjustments were done accordingly with follow-up of pharmacokinetics and safety. For the haemodialysis patient, an initial dose of 250mg was administered, which corresponds with approximately half the dose required to achieve the target AUC in a typical individual without renal function. The patient with moderate renal impairment initially started with conventional BSA-based dosing (755mg).

Results: For the haemodialysis patient, the AUC after the first 250mg dose was estimated to be 230mg*h/L. Therefore, the dose was decreased to 200mg and maintained during subsequent cycles. The estimated AUC during these cycles was 185mg*h/L, which was within the therapeutic window. Therapy was well-tolerated: no dose-limiting toxicity was observed. We found that during haemodialysis pemetrexed clearance increased three-fold (from 1.00L/h to 3.01L/h), which approximates normal clearance of pemetrexed (the typical pemetrexed clearance in the population with adequate renal function is 5.4L/h ±19.3% CV). The AUC after the BSA-based dose for the patient with renal impairment was estimated to be 260 mg*h/L. This was considerably higher than the target exposure, thus the dose was reduced to 500mg. At the subsequent pharmacokinetic evaluation, the estimated AUC was 166mg*h/L. The dose was maintained at 500mg at the following cycles and therapy was well-tolerated: no dose-limiting toxicity was observed.

Conclusions: With these cases we demonstrate that pharmacokinetically-guided dosing of pemetrexed seems to be a feasible strategy to allow for safe treatment and a proven effective systemic exposure to pemetrexed in patients with renal impairment and lung cancer. Optimal systemic exposure was reached after dose adjustment and pemetrexed was well tolerated. Furthermore, this is the first report on pemetrexed pharmacokinetics during haemodialysis. We demonstrated that during haemodialysis, clearance approximates normal clearance of pemetrexed. Our results encourage further evaluation of individualized dosing of pemetrexed in a prospective clinical study in patients with renal impairment who are currently often withheld pemetrexed treatment.

Development and validation of a limited sampling strategy for pemetrexed therapeutic drug monitoring and research purposes.

Introduction: Pemetrexed is indicated for the treatment of non-small cell lung cancer and mesothelioma. For pemetrexed there is a well-established exposure-toxicity relationship. Currently, pemetrexed is dosed based on body surface area (BSA), but BSA-based dosing ignores the impact of renal function (the main determinant for exposure), which leads to a large variability in systemic exposure. To further optimize treatment with pemetrexed, therapeutic drug monitoring may be a feasible strategy. For statistical considerations, intensive pharmacokinetic sampling during a long interval is desired. However, from a patient perspective, a minimally invasive strategy is desired in a small time window. Therefore, our goal was to develop a limited sampling strategy (LSS) for assessment of pemetrexed clearance.

Method: Using a validated pharmacokinetic model, a dataset of 2,000 individuals with varying renal functions was simulated with NONMEM. The obtained clearances for these individuals were considered as 'true values'. Subsequently, various LSSs were evaluated to estimate clearance in patients with adequate and impaired renal function. Accuracy and precision were assessed with mean relative prediction error (MPE) and normalized root mean squared error (NRMSE). We defined an acceptable LSS as: maximum 4 sampling time-points within 8 hours and an MPE and NRMSE <15% for prediction of clearance. Finally, the most suitable LSS for patients with adequate renal function was externally validated with a rich pharmacokinetic dataset of 15 pemetrexed patients (from ZonMW project 152001017). The real-life rich PK-data were used as 'true values' and used as reference for the estimated clearances.

Results: The in silico evaluation for patients with an adequate renal function, demonstrated that a sampling schedule of 0.5-2-4 hours after pemetrexed administration resulted in an acceptable MPE of -4.78% and NRMSE of 13.37%. A schedule of sampling at T= 0.5-2-8 resulted in an MPE and NRMSE of -5.41% and 12.97%, respectively. The external validation with the real-life data showed that a 3-sample schedule at 0.5-2-4 hours after pemetrexed administration resulted in an MPE and NRMSE of -4.16% and 7.10%. Sampling at 0.5-2-8 hours resulted in MPE and NRMSE of -3.95% and 6.09%. For patients with impaired renal function, a sampling schedule of 0.5-2-8 hours gave an acceptable MPE and NRMSE of -5.41% and 12.97% . With 3 samples at 0.5-2-4, the NRMSE exceeds 15% (15.95%) with an MPE of -4.87%. No real life data were available for patients with renal dysfunction, as pemetrexed is contraindicated in this group.

Conclusions: We performed an in silico evaluation to establish a LSS for pemetrexed and validated this with real-life data. Three sparse samples at 0.5, 2 and 4 hours should suffice for estimation of pemetrexed clearance with normal renal function. With decreased renal function an extended sampling schedule (up to 8 hours) is required. We are currently using the developed LSS for dose individualization in routine clinical practice and in a prospective clinical trial.

Novel online drug-drug interaction resource reveals clinically relevant interactions in >20% of the searches

Background: Patients with cancer treated with oncolytics are at risk of experiencing a drug-drug interaction (DDI) between their oncolytics and co-medications. DDIs affect nearly 60% of patients on therapy of whom 16% experiences a major event. In approximately 4% of the cancer patients a DDI is the cause of death. To facilitate the safe prescription and use of oncolytics, the freely available website www.cancer-druginteractions.org was introduced. We hereby present the results of the use of this online DDI resource during the first year since the launch on June 1st 2017.

Methods: The DDI potential for the most frequently used co-medications (>400) in cancer patients was reviewed based on registration documents and scientific literature. A simple "traffic light" system was used to warn for the interaction potential. Background information and level of evidence is provided in the summary for each interaction. Since the launch of the website the demographic use, the number of unique visitors and the number and severity of the interactions consulted are monitored every 3 months. Website development was made possible by educational grants.

Results: A total of 43 targeted oncolytics, representing 29 targeted oral oncolytics and 14 monoclonal antibodies (MoABs) for different malignancies, have been added to the website since the start of the project (2017). Currently 17,286 interaction-pairs have been included on the website. In the past 12 months a total of 18,189 searches were performed by 5,250 unique visitors from 44 different countries. Most of the DDI queries were entered by individuals from the United Kingdom (58%) and the Netherlands (20%), since the website was most widely promoted in these countries thus far. Eighty percent of the searches were performed for oral oncolytics and twenty percent for MoABs. A potential interaction which required action of the prescriber was shown in 23% of the performed searches. The most frequently checked co-medications classes were antibacterials, analgesics and gastrointestinal agents. The most frequently checked oncolytics were enzalutamide (9.7%), axitinib (6.5%) and bevacizumab (6.5%). Recently, on September 1st 2018, we launched 'Cancer iChart', a user-friendly app available for both Android and iOS devices.

Conclusion: Thus far, the DDI checker is being used worldwide. Almost a quarter of the 18,189 performed searches showed a clinically relevant interaction. The freely available website and app will facilitate health care professionals' awareness of potential DDIs between oncolytics and frequently used co-medications. This supports safe prescription of oncolytics and co-medications in patients with cancer.

Novel Niclosamide Stearate Nanoparticles Induce Lysosome Membrane Permeabilization in Triple Negative MDA-MB-231 Breast Cancer Cells

Background: Niclosamide (Ni), an FDA approved anthelmintic drug, has recently shown to exhibit anticancer effects. Due to a limited water solubility, its oral bioavailability is low. Therefore, new formulations are required to re-appropriate Ni as an anticancer drug.

Cancer cells eat more Low-Density Lipoprotein (LDLs) and folic acid than normal cells, due to overexpression of their receptors. Inspired by these endogenous processes, our laboratory has produced stealth and folate-targeted nanoparticles (SNPs and FNPs, respectively) of 20-30 nm in size, which are composed of the pro-drug niclosamide stearate, encapsulated in a lipid monolayer (NSNPs).

Ni has been shown to produce cytosolic acidification (CA) in cancer cells. However, the mechanism by it occur remains elusive. Lysosome membrane permeabilization (LMP) can lead to CA and it is triggered by different stimuli. We hypothesize that by esterifying Ni and coating it with a lipid monolayer, we can mimic the body's transport system to effectively deliver hydrophobic drugs to cancer cells. The NSNPs will thus be taken up by cancer cells via endocytic pathways and gain access to the lysosomes, causing LMP.

This study therefore analyses and compares whether and to what extent, Ni and NSNPs induce LMP in breast cancer MDA-MB-231 and non-cancer MCF-12A cells as a function of its concentration, incubation time, and FBS percentage.

Materials & Methods: NSNPs were prepared using the rapid solvent injection method developed by our laboratory. MDA-MB-231 and MCF-12A cells were treated with Ni, SNPs and FNPs in the concentration range of 1-200μM for 24, 48 and 72h, in culture media containing 2%/10% FBS. LMP was detected by staining fixed cells with the galectin-1 antibody followed by Alexa-Fluor488-conjugated secondary antibody and DAPI (nuclei staining). Fluorescent images were obtained with an Olympus microscope (x40 objective). Quantification of galectin-1 puncta formation was performed by manual counting of 10 fields per sample. Statistical analysis was performed by multiple t-tests.

Results: Our findings showed that Ni, SNPs and FNPs all induce LMP in MDA-MB-231 cells. The percentage of cells with galectin-1 puncta formation (lysosome leakage marker) increased as the concentration of Ni and NSNPs increased (direct relation). It was also directly dependent on the incubation time. However, it was inversely dependent on the FBS concentration, showing percentage of cells with galectin-1 puncta formation comparable with positive controls at the lowest FBS percentage analysed. Interestingly, the formulations induced low percentages of MCF-12A cells with LMP compared with MDA-MB-231 cells. The few effects observed in MCF-12A cells were not affected by the FBS percentage.

Conclusions:Ni and NSNPs accomplished its LMP effects preferentially on MDA-MB-231 cells. Interestingly, we found that LMP is inversely proportional to the FBS concentration in MDA-MB-231 cells. Results suggest that the FBS components (such as albumin, LDLs) could be competing for the endocytic pathways that transport the formulations into the cells, leading to a lower effect of Ni and NSNPs when the FBS percentage increases. They also suggest differences between cancer and non-cancer cells that modulate the timing in which LMP takes place, and influences of serum proteins on NSNPs uptake.

A generalisable pharmacokinetic-pharmacodynamic (PKPD) model of savolitinib, a novel MET tyrosine kinase inhibitor, to explore extent and duration of target inhibition required for optimal efficacy across a range of tumour xenograft models

Background
MET is a transmembrane tyrosine kinase receptor that is dysregulated in multiple cancer types. Savolitinib (AZD6094, HMPL-504, volitinib) is a potent (IC50 4 nM) and highly selective MET tyrosine kinase inhibitor being developed for papillary renal cell carcinoma (PRCC) and non-small cell lung cancer (NSCLC). In preclinical xenograft models, savolitinib demonstrated rapid and extensive inhibition of phosphorylated-MET (pMET) with an EC50 of 0.35 ng/ml, and anti-tumour activity in MET-amplified models (RCC-43b and RCC-47 for PRCC; MKN-45, SNU-5 and Hs746T for gastric cancer; EBC-1 for NSCLC).

Materials and Methods
Anti-tumour activity of savolitinib was investigated in EBC-1 xenografts under a range of dosing schedules and conditions. A population PK model was developed to predict the level and duration of pMET inhibition required for tumour shrinkage. The modelling objectives were to (1) determine whether a generalizable model can be applied to EBC-1 and data from other cell-lines investigated, and (2) Determine the extent and duration of pMET inhibition that delivers optimal efficacy.

Results
EBC-1 xenografts were treated with savolitinib at 30 mg/kg daily (76% tumour growth inhibition [TGI]), every other day (43% TGI), or 4 days on/3 days off (39% TGI). Intermittent dosing was also explored at 100 mg/kg every other day (80% TGI), 4 days on/3 days off (67% TGI) and 2 days on/5 days off (46% TGI). To assess effects of prolonged pMET inhibition, twice daily dosing at 15 mg/kg (83% TGI) and 30 mg/kg (94% TGI), and co-dosing savolitinib at 15 mg/kg with the cytochrome P450 inhibitor, 1-aminobenzotriazole was also tested (61% regression). In the population PK-pMET-TGI model, savolitinib plasma concentration drove pMET inhibition and, in turn, TGI. The effect (E) of pMET suppression on tumour kill rate was modelled as proportional to the growth rate of the cell line so that a single set of effect parameters could describe the effect in several cell lines with differing growth rates. E thus became a factor of the intrinsic growth rate of the tumour model rather than a kill rate constant. When E=1, the kill equals the growth and tumour stasis is reached, and during the periods where E>1, kill is greater than growth and the tumour shrinks. By scaling kill to growth, the model was able to partially explain the observed heterogeneous tumour responses across different tumour models. The remaining heterogeneity in tumour response was explained by different sensitivity to pMET inhibition. The final model described the relationship between pMET inhibition and tumour shrinkage, with a minimum of 80% and 97% sustained inhibition of pMET required for net tumour shrinkage in the most and least sensitive tumours, respectively.

Conclusions
Estimating drug effect relative to tumour growth rate offers a novel way in which to apply a mathematical model with parameters of drug effect that are shared across different cell-lines and PDX models. The developed model offers the potential to be translated to predict the expected tumour growth inhibition in humans under varying dose regimens by accounting for mouse-to-man differences in PK and tumour growth dynamics.

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Translation from mouse to human of pharmacokinetic-pharmacodynamic modelling of biomarker response – learnings from the AstraZeneca Oncology portfolio

Objectives:
Pre-clinical data and predictive modelling are extensively used in support of candidate drugs taken into the clinic. This includes the prediction of human dose anchored upon an understanding of the level of target modulation required to drive efficacy in an animal model. Once in the clinic, emerging exposure data from phase 1 patient studies are benchmarked against pre-clinical insights and clinical biomarker data to assess proof-of-mechanism criteria. Given the extensive implementation across the industry of model based solutions to predict human dose, it is perhaps surprising that there are relatively few publications reporting an analysis that evaluates the pre-clinical to clinical translation of PKPD relationships. This work presents such an analysis looking across a number of AstraZeneca Oncology agents and examines how pre-clinical data / models translate to clinical pharmacodynamic response.

Methods:
A framework has been established to enable an objective evaluation for the translation of an exposure-response relationship from an animal model to that observed in human for pharmacodynamic biomarkers. Inclusion criteria for evaluation were driven by (1) the availability of sufficient clinical data (derived from tumour or peripheral surrogate tissue) to enable a derivation of EC50; (2) a PD biomarker measured both in the animal model used and the clinic.

Results:
Overall, for the six case studies presented here there is a strong relationship observed, with an EC50 within 2 to 5 fold between mouse and human. The clinical datasets were naturally constrained compared to the pre-clinical datasets in terms of the intensity of data available, particularly for tumour PD. Therefore, in the majority of cases it was not possible to derive a robust exposure vs. response relationship using patient tumour samples. In contrast, PD data from peripheral tissues offered greater depth of data (time points, doses) to enable a comparison against mouse tumour PD. Measuring the time-course of PD effects in surrogate tissue offers the additional benefit of demonstrating duration of effect relative to plasma PK.

Conclusions:
This exercise has demonstrated that pre-clinical tools and pharmacokinetic-pharmacodynamic modelling can robustly predict human exposure-response relationships for target engagement biomarkers. This offers the opportunity to integrate a more intensive data set generated in mouse, with relatively sparse clinical PD data during dose escalation to exposure and PoM criteria. Nevertheless, attrition in the clinic continues to be dominated by lack of efficacy, and therefore, much work is still required to improve the translation and prediction of human drug efficacy, linking target modulation to effects on disease biology.

Effect of patient characteristics on pharmacokinetics of enzalutamide in mCRPC patients

Background: Enzalutamide is an oral anti-androgen drug that is widely used for treatment of (metastatic) castration resistant prostate cancer (mCRPC). Currently limited pharmacokinetic data are published on patients treated with enzalutamide in an outpatient setting. In the pharmacokinetic analysis of phase III clinical trials, the effect of patient characteristics on enzalutamide exposure was evaluated, however this may not be extrapolable to a more heterogeneous patient population in daily practice. We hypothesized that weight/lean fat mass ratio and age could be of influence on enzalutamide pharmacokinetics. In this analysis the effect of age and body composition on enzalutamide and its active metabolite N-desmethyl enzalutamide exposure is determined.

Material&Methods: Pharmacokinetics data from two studies (ANDROPS and ILUMINATE) with enzalutamide in mCRPC patients were pooled. In a cohort study (ANDROPS) random plasma samples were prospectively collected from 39 patients. Samples collected on steady-state (>35 days) were included for this analysis. Since peak-to-trough ratio is small for enzalutamide (1.25) and median time to sample collection after drug intake was 16.5h (3.5-24.5h) random samples were accepted for this analysis without extrapolation to trough plasma concentrations (Cmin). The median time to first sample collection for ANDROPS was 92 days (range 40-937days). In the ILUMINATE study enzalutamide plasma samples (Cmin) were collected in 40 patients. The plasma samples taken 6 months after start of treatment were used for this analysis, since this collection moment was best comparable to the ANDROPS cohort. All patients used 160mg enzalutamide once daily. Age and bodyweight(BW) at baseline were used in this analyses. Before the data from both studies were pooled, the distribution of pharmacokinetic data and patient characteristics were tested for differences. Fat free mass (FFM) was calculated with a previously published formula [1]. The ratio of BW/FFM was used as descriptor of body composition. Spearman's rank correlation was calculated for the sum concentrations (enzalutamide plus N-desmethylenzalutamide) in relation with age and BW/FFM.

Results: No significant difference between the plasma concentrations, age, BW and FFM between both studies were identified. Therefore the results from all 64 mCRPC-patients (31 ANDROPS; 31 ILUMINATE) were pooled. Median(range) plasma concentrations were 12.6 mg/L (6.8-19.7mg/L) and 12.3 mg/L (7.3-23.4mg/L) for enzalutamide and N-desmethylenzalutamide, respectively. Medians(range) of age and BW/FFM were; 71y(50-86) and 1.34(1.15-1.57). Spearman's correlation coefficients was r=0.06 (p=0.64) for age and sum concentrations and r= -0.15 (p=0.24) for the ratio BW/FFM and sum concentrations.

Conclusions: To our knowledge, this is the first analysis of enzalutamide pharmacokinetics in patients with mCRPC in the heterogeneous outpatient setting. No association with age or body composition (BW/FFM) and enzalutamide + N-desmethylenzalutamide plasma concentrations was observed. These results are in line with the earlier population pharmacokinetic analysis. Based on these results, no a priori dose adjustments of enzalutamide appears necessary for elderly or obese mCRPC patients.

[1] S. Janmahasatian et al. Quantification of Lean Bodyweigth. Clin Pharmacokinet 2005; 44(10:1051-1065).

Mechanistic models of cancer-immune cycle and immunotherapies

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Cancer is characterized by the accumulation of a variable number of genetic alterations acquired by the cells overtime and the subsequent loss of normal cellular regulatory processes. These events result in the expression of neoantigens that are then presented by major histocompatibility complex class I (MHCI) molecules on the surface of cancer cells, which stimulates the immune system to respond against it. The heterogeneity of neoantigens expressed on the surface of cancer cells (due to continuous and rapid genetic alternations), and negative regulators of immune systems are the major limitations in the treatment of cancer.

Cancer immunotherapy, where treatments mobilize the patient's own immune system to fight cancer and provide lasting therapeutic benefit, is the fastest developing area of oncology. New therapies are aimed at targeting different stages of the Cancer-Immunity Cycle, which involves a dynamic system of non-linear interactions between cellular and molecular players in immune system and tumor. The Cancer-Immunity Cycle involves a series of events following the expression of neoantigens by cancer cells. The neoantigens are captured by Dendritic Cells (DCs) and other Antigen Presenting Cells (APCs) infiltrating the tumour microenvironment. The DCs/APCs migrate to lymph node and present antigens to T-cells, resulting in the priming and activation of effector T cell responses against the cancer-specific antigens. The activated cytotoxic T-cells traffic to tumour microenvironment, specifically recognize, bind and kill target cancer cells, thus closing the positive feedback loop of antigen release, antigen presentation and T-cell activation which magnifies anti-tumour response. In order to prevent the immune system from attacking its own cells, this feedback is under tight control of various checkpoint mechanisms. Tumours that successfully establish usually exploit these checkpoints to suppress the immune response.

Drug development decisions require quantitative and mechanistic understanding of the Cancer-Immunity Cycle. The design of an effective cancer immunotherapy is complicated by various factors, including a potentially immunosuppressive tumour microenvironment, immune-modulating effects of conventional treatments and therapy-related toxicities. These complexities incorporated into the mathematical models can aid in providing mechanistic insights, rational therapy design and development decisions. Here, we systematically survey 136 published mechanistic models describing various components of Cancer and Immune System dynamics. We distill and discuss several example models that have grown in complexities, highlighting how model development interlinks the advances in cancer-immune biology. This comprehensive review of literature models on cancer-immune cycle can potentially benefit modelling efforts in pharmaceutical industry.

PK/PD model for describing the antitumor effect of anti-PD-L1 mAb administered to melanoma bearing mice.

Background: Immunotherapy has changed the landscape of cancer treatments. The understanding of tumor immunology has highlighted the role of the immune system in controlling tumor proliferation. Immune checkpoint pathways, in particular, the axes PD-1/PD-L1, is involved in mechanisms of tumor resistance by down-regulating the cytotoxic T cell activity. The incorporation of specific monoclonal antibodies (mAb) to block PD-L1 can promote and reestablish innate and adaptive immune effector mechanisms to enhance the anti-tumor immune response. However, the inter-individual variability, ranging from responders to non-responders has led to investigate in a mechanistic manner the relationship between anti-PD-L1 mAb exposure and the therapeutic effect applying PK/PD models. In this way, syngeneic murine models represent useful tools for exploring this approach. Therefore, the aim of this work was to integrate in a mechanistic PK/PD model data of tumor growth and body disposition of anti-PD-L1 administered to tumor bearing mice, to get a predictive description of the antitumor effect according to the presence of certain immune biomarkers.

Material & Methods. C57BL/6 female, s.c. inoculated with B16-OVA cells, were used for several experiments: i) Tumor growth data: control and three treated groups receiving i.v. 100 μg/mouse (Q3D x 4) of Anti-PD-L1 mAb at day 3,7 and 11 after tumor cell inoculation were monitored for 40 days; ii) PK data: after 7 days of cell inoculation, mice received a single dose of anti-PD-L1 for measuring mAb concentrations in serum and tumor over 72h and iii) in a parallel experiment with the same design as for PK data, tumor biomarkers, such as CD8+-OVA, PD-1 and PD-L1 expression, were quantify by cytometry in control or treated animals. Data were log transformed and a sequential approach was followed developing first the PK model and then, the PK/PD model. The analysis was done with NONMEM 7.3. and R program for data manipulation and graphical representation.

Results. Anti-PD-L1 disposition was described by one compartment model. Tumor concentrations were well captured assuming distribution from the serum compartment through a first order distribution rate constant and enabling first order elimination at the tissue target. Distribution to the tumor was considered negligible for serum PK analysis. All tumor size measurements were analyzed simultaneously using the Simeoni's tumor growth inhibition model. Drug effect on tumor cell death was implemented through a delay compartment which accounts for the signal triggered by the PD-L1-mAb binding in tumor cells followed by the complex internalization. Additionally, an indirect mechanism due to the presence of immune biomarkers in microenvironment was identified for an adequate description of tumor shrinkage.

Conclusion. The anti-tumor effect of anit-PD-L1 in tumor bearing mice was described by a PK/PD model that combined a direct and indirect mechanisms triggered by the drug binding to tumor cells and the subsequent activation of cytotoxic immune cells, influencing the antibody activity.

Polymeric Micelles-based Nanomedicines: Suitable Modulators of Drugs' Pharmacokinetics and Pharmacodynamics

Background: Nanotechnology emerged as a promising strategy to improve the therapeutic outcomes as well as to circumvent the limitations related with the conventional drugs. Among the different Nano-systems, micelles composed by amphiphilic polymers (PM), such as poloxamers, received increased attention as enhancers of drug solubility, bioavailability, stability and biodistribution. Owing to its small size, PM are poorly recognized by reticuloendothelial system (RES), presenting long half-lives. Also, they suffer passive targeting to solid tumor sites by the so-called enhanced permeability and retention (EPR) effect, improving the pharmacokinetic of the loaded drug and reducing the off-target cytotoxicity. Interestingly, these polymers have shown to interfere with the function of P-glycoprotein, being a useful strategy to overcome drug-resistance.

Materials & Methods: PM physicochemical characterization was performed through Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM). The encapsulation efficiency was measured by High Performance Liquid Chromatography (HPLC). The internalization in different cancer and non-cancer cell lines was performed through flow cytometry and the cytotoxicity assessed by a Tetrazolium-based assay (MTT). The in vivo studies were performed accordingly the ethic committee of Vall D'Hebron Research Institute. The maximum tolerated dosis (MTD) were performed by administration of different PM concentrations at healthy nude female mice, once a week and three times a week during 3 weeks. The extravasation and biodistribution were performed in pancreas and breast cancer orthotopic models, respectively.

Results: The proposed PM present a mean diameter around 26 nm, a low polydispersity index (< 0.2) and a neutral zeta potential. The encapsulation efficiency of the present nanoparticles were tested for different hydrophilic and hydrophobic drugs and was always higher that the 95%. In vitro assays demonstrate that PM can be easily internalized by cells before 4 hours of incubation being the encapsulated drug usually more effective than the free drug. The in vivo toxicity was tested at different therapeutic regimens and no adverse effects were detected. It was also demonstrated their biocompatibility in blood and the continuous drug release in plasma. The extravasation studies demonstrated that the PM are able to leave blood circulation and easily penetrate the tumor. These result was confirmed with the biodistribution studies where it was shown an accumulation of more than 10% in tumor, only due to the EPR effect. Accumulations of around 15% in liver and lungs were also detected, what make them suitable for treatments in these organs. Due to the residual accumulation of PM in muscle and heart, the PM have the ability to reduce the muscular and cardio toxicity associated to some drugs.

Conclusion: The tailorable size, loading and drug release profile of the proposed PM make them a suitable platform to encapsulate different types of drugs and deliver them through different administration routes. Therefore, it is foreseen that the present PM-based approach for drug delivery will allow the development of new anti-cancer therapies with reduced side effects and increased efficacies.

Targeted Gene Delivery Systems: A Nanomedicine Approach for Breast Cancer Cells Treatment

Background: In recent years, nanomedicine has evolved aiming to achieve great advances in cancer treatment and diagnosis. New polymeric materials such as polymeric micelles (PM) have been employed in order to overcome stability and release-related problems associated with drug molecules. Due to its high specificity, gene therapy has appeared as a promising alternative for an effective and specific treatment of complex diseases. Using RNA interference (RNAi) technology, concretely small interfering RNAs (siRNA) it is possible to silence gene expression. However, siRNA alone by itself cannot induce RNAi mechanism due to low cell interaction, unspecific cell target and low stability within bloodstream. Combination of PM and siRNA technology would allow to overcome the above mentioned drawbacks. Furthermore, PM surface conjugation with cetuximab, a specific antibody against epidermal growth factor receptor (EGFR), would enhance PM internalization into EGFR overexpressing cancer cells.

Materials & Methods: Polymer chemical group modification was characterized through FT-IR and 1H-NMR analysis. PM physicochemical characterization was performed through Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM). Entrapment efficiency was measured by a Nanodrop NP-2000. The internalization of PM in breast cancer cell lines was performed through flow cytometry and the cytotoxicity assessed by a Tetrazolium-based assay (MTT). Hemocompatibility studies were performed by the ICTS "NANBIOSIS", at the CIBER-BBN's in vivo Experimental Platform of the Functional Validation & Preclinical Research (FVPR) (Barcelona, Spain) using human blood samples from healthy volunteers. Silencing efficacy assays were studied by RT-qPCR.

Results: The polymer by which PM is constituted was chemical modified in order to attach cetuximab onto PM surface. IR and 1H-NMR confirmed the exchange of OH by COOH group with a band appearance at 1725 cm-1 and a signal at 4.36-4.38 ppm, respectively. Also, gelatin, a biocompatible cationic polymer, was used to complex siRNA. The proposed PM presents a mean diameter around 32 nm, a proper polydispersity index (around 0.270) and a positive zeta potential to interact with negative siRNA molecule structure. Moreover this increase in overall charge is essential to allow an effective siRNA entrapment as was demonstrated by the obtained high entrapment efficiency (> 85%). In vitro assays demonstrate that PM conjugated with cetuximab internalized faster in EGFR overexpressing cancer cells (MDA-MB-231) than PM. Conversely, non-EGFR expressing cancer cells (MCF-7) showed no differences in the internalization profile between PM and PM-cetuximab. Hemocompatibility assessment showed optimal results in the effect of polymer on red blood cells integrity (< 5% of damage) and plasma coagulation (< 13.4s of coagulation time for prothrombin). Silencing studies exhibited low gene expression levels after siRNA transfection compared with siC.

Conclusion: The optimal size, surface charge and easy chemical functionalization, together with the biocompatibility and biodegradability of the used polymers as well as the simple preparation method of PM make them a suitable platform for targeted gene therapy into cancer cells. The enormous flexibility endorsed by the proposed PM to formulate different types of active substances is expected to give an important contribution for the nanomedicine field applied to different diseases.

Food intervention to make therapy with pazopanib more patient friendly and affordable

Background Pazopanib has been registered for advanced soft tissue sarcoma (STS) and metastatic renal cell carcinoma (mRCC) and is used in a fixed oral dose of 800mg taken fasted. However, ingesting pazopanib with food, is a more patient friendly approach. Moreover, the occurrence of well-known gastro-intestinal (GI) side effects like diarrhea, makes fasted intake even more challenging and could potentially be diminished when pazopanb is taken with food. Simultaneous intake with food results in better pazopanib absorption. Therefore, a reduced dose could result in similar exposure, reduction of GI side effects and reduction of healthcare costs. The aim of the initial part of the study was to establish the bio-equivalent dose of pazopanib taken with a continental breakfast (CB), compared to the standard intake of 800mg in fasted state. The aim of the second part of the study was to evaluate patients preference for either intake regimens. Furthermore, the occurrence of GI side effects under both intake regimens was investigated.

Methods This study was divided into two parts. First a phase I cross-over multi-center pazopanib pharmacokinetic (PK) study in STS and mRCC patients was performed to establish the bio-equivalent pazopanib dose when ingested with a CB. Patients were treated with 800mg pazopanib in a fasted state, followed by 600mg ingested with a CB. Bio-equivalence was assumed when the Geometric Mean Ratio (GMR) (fed/fasted) of the AUC0-24h and Cmax and their 90% confidence interval (CI) were within the range of 0.8 and 1.25. After that the bio-equivalent dose was determined, the safety study started. This study was designed as a randomized, multicentre, cross-over study. Patients were assigned to start either with 800mg fasted followed by 600mg with CB or visa versa during one month each. After the two treatment periods, patients preference was asked. Treatment satisfaction was monitored using the Cancer Therapy Satisfaction Questionnaire (CTSQ). The following outcomes were scored: Feelings about side effects (FSE), Satisfaction of therapy (ST) and Expectation of therapy (ET). Additionally, patients kept a diary to monitor the occurrence of diarrhea (e.g. number of stools per day,).

Results For the bio-equivalence study 19 patients were enrolled, of whom 16 were eligible for PK analysis. GMR (fed/fasted) AUC0-24h was 1.09 (CI 1.02-1.17) and GMR Cmax was 1.12 (CI 1.04-1.20). In the safety study 75 patients where included of whom 58 patients were eligible for safety analysis. The FSE-CTSQ and ST-CTSQ were significantly improved when 600mg was ingested with a CB compared to 800mg fasted (FSE-CTSQ score of 71 vs 64 (p=0.03) and ST-CTSQ score of 86 vs 81 (p=0.05), respectively). ET-CTSQ was not evaluated differently between both groups. Furthermore, 70% of the patient preferred the use of 600mg pazopanib with CB while 7% of the patients had no preferred intake regimen and 23 % of the patient preferred the fasted intake. No difference in the number of stools (1.7 vs 1.7 (CI -0.05-0.2) was observed between both intake regimens.

Conclusions By a simple food intervention a 25% reduced dose of pazopanib can be used. The intake with food improves patients therapy satisfaction. Most patients in this study choose to continue using pazopanib with food, emphasizing the patient friendliness of this approach for patients with STS and mRCC. Lastly, this approach may contribute to keep oncolytic therapy, such as pazopanib, more affordable and thus probably more available to all patients.