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GROUPE DE PHARMACOLOGIE CLINIQUE ONCOLOGIQUE

GPCO unicancer

édito

Chers collègues, chers membres du GPCO,

L'ensemble du bureau du GPCO vous adresse ses meilleurs vœux pour 2020.
Que cette nouvelle année soit riche en projets collaboratifs pour notre groupe, en avancées significatives pour vos activités de recherche et hospitalière , et en moments partagés autour de la pharmacologie en oncologie !

Bonne lecture,
Le Bureau du GPCO

Collaboration entre le GPCO et le Groupe Immuno-Oncologie d'Unicancer

Suite à la dernière réunion du GPCO, Fabienne Thomas a pris contact avec le Pr. Jean-Pierre Delord qui s'est dit très favorable à la mise en place d'une collaboration entre GPCO et GIO sur des thématiques telles que notamment les reports de dose, des réflexions autour des schémas d'administration.
Certaines études, en cours de rédaction, pourraient tout à fait servir de base pour initier ce genre de travaux.
Un groupe de travail sera prochainement mis en place. Parmi les thématiques à aborder :

- **Faire un état des lieux des molécules dosées et des laboratoires.**
- **Réflexion pour mettre en évidence une ou 2 questions prioritaires à partir desquelles des études ancillaires pourraient être proposées au GIO.**

Si vous souhaitez en faire partie, vous pouvez contacter Audrey Bellesœur (audrey.bellesoeur@curie.fr) ou Joseph Ciccolini (ciccolini.joseph@gmail.com).

Actualités

- **Dernière réunion du GPCO le 11/12/19 : Télécharger le compte-rendu ici**
- **Prochaine réunion du GPCO : jeudi 25 juin 2020 de 10h à 12h30. Pour confirmer votre présence, merci d'utiliser ce lien.**
- **Ateliers du GPCO, le 10 mars 2020, au CHU de Montpellier, sur la thématique du génotypage du CYP2D6 et de son application pratique. Il est encore temps de vous inscrire, contactez jean.christophe.boyer@chu-nimes.fr**
- **Mise en place d'un groupe de travail sur les adaptations de doses des anticancéreux chez les enfants (obèses), en collaboration avec la SFCE (Société Française de lutte contre les Cancers et les leucémies de l'Enfant et de l'adolescent). Si vous souhaitez en faire partie, contactez Thomas.Fabienne@iuct-oncopole.fr.**
- **Le projet FUSAFE-3 n'a pas été accepté lors de l'évaluation des projets complets pour le PHRC-K. Des pistes alternatives de financement sont en cours d'études.**

Atelier 2020 : le génotypage du CYP2D6 et son application pratique

Il reste une dizaine de places, mais le séminaire est maintenant ouvert également aux personnes non-membres du GPCO. Il faut que les retardataires se dépêchent.
Nous avons la chance exceptionnelle de pouvoir accueillir Andréa Gaedigk, pionnière dans l'implémentation du score d'activité du CYP2D6. Elle est membre du board de pharmGKB, très proche de celui du CPIC et de PharmVar. C'est une chance de pouvoir faire reconnaitre le dynamisme de notre groupe, le GPCO, à l'international car nous espérons par son intermédiaire avoir une porte d'entrée vers les groupes de travail de la PGx Internationale.
Nous accueillerons également un clinicien Suisse, le Pr Desmeule, médecin interniste, spécialisé dans la prise en charge de la douleur. Il dirige un service de médecin personnalisée qui fait appel à la génétique et à la PK, notamment dans la prescription des opioïdes.
Enfin, Fabienne Thomas présentera les résultats du projet PHACS (CYP2D6 et tamoxifène).
L'atelier se conclura, l'après-midi, par une mise en pratique des conférences de la matinée par des approches de bio-informatique.

Harmonisation des pratiques de prévention des effets indésirables graves liés à la néphrotoxicité du méthotrexate haute dose en France et réévaluation des critères d'octroi de l'antidote VORAXAZE®

A la suite de la réunion de concertation tenue en octobre 2018 entre l'ANSM, le LYSA (Lymphoma Academic Research Organisation), l'INCa (Institut National du Cancer) et les CRPV (Centres Régionaux de Pharmacovigilance) en charge de l'enquête de PV, il a été décidé de :

- Rédiger un point d'information et une check-list à destination des professionnels de santé afin de rappeler les modalités pratiques d'utilisation du méthotrexate haute dose (MTX-HD)
- Réévaluer les critères d'octroi des ATUn de VORAXAZE®.

A cet égard, l'ANSM a sollicité l'avis et l'expertise du GPCO (par le biais d'Etienne Chatelut et de Gérard Milano) fin mai 2019 ; l'objectif final de ce travail étant d'aboutir à la mise en place :
D'une information sur les modalités pratiques d'utilisation du MTX-HD, proposant notamment :

- Les durées et vitesses de perfusion recommandées pour l'utilisation du MTX-HD
- La surveillance précise de la fonction rénale des patients, avant et après le traitement
- Les modalités d'hydratation et de diurèse alcaline (délai d'initiation, volume, durée, …)
- La surveillance du pH urinaire et de la diurèse, avant pendant et après l'administration
- La surveillance de la méthotrexatémie (fréquence de dosage et poursuite de la surveillance)
- Le sauvetage par l'acide folinique (rappel de la voie d'administration, dose, adaptation de la dose à la surface corporelle ou à la méthotrexatémie)
- De critères d'octrois pour l'ATUn Voraxaze®, réévaluer au regard des différentes référentiels existants.

Un groupe de travail, animé par Etienne CHATELUT (Pharmacologue, Institut Universitaire du cancer – Toulouse) et Gérard MILANO (Pharmacologue, Centre Antoine Lacassagne, Nice) a été constitué.

Y ont participé : Julie ABRAHAM (Onco-hématologue, CHU Limoges), Sophie BROUTIN (Pharmacologue, Institut Gustave-Roussy, Villejuif), Stanislas FAGUER (Néphrologie, CHU Toulouse), Lauriane GOLDWIRT (Pharmacologue, Hôpital Saint-Louis, Paris), Florence NETZER (Pharmacien Hospitalier, Institut Gustave-Roussy, Villejuif), Emmanuel RAFFOUX (Hématologue, Hôpital Saint-Louis, Paris), Florent PUISSET (Pharmacien Hospitalier, Institut Universitaire du cancer – Toulouse), Lucie OBERIC (Hématologue, Institut Universitaire du cancer – Toulouse), Julien ROSSIGNOL (Hématologue, Institut Gustave-Roussy, Villejuif) Suzanne TAVITIAN (Hématologue, Institut Universitaire du cancer – Toulouse), Jean-Baptiste WOILARD (Pharmacologue, CHU Limoges).

A l'issue d'une analyse de la bibliographie, des recommandations existantes et d'un bilan des pratiques, les membres du groupe considèrent que l'augmentation de la créatininémie de 50%, observée à tout moment durant la période optimale d'administration du Voraxaze® (soit 60 h après le début de la perfusion de méthotrexate) par rapport à la valeur de base est un critère recevable pour poser les indications du Voraxaze®. Cependant il devrait être complété par une valeur critique de méthotrexatémie, valeur dépendante de l'échéance à laquelle on se situe H24 ou H48 après le début d'une perfusion de MTX de durée de 3 à 8h, H32 ou H48 quand il s'agit d'une perfusion de 24h. Pour l'échéance H48, Ramsey et al suggère 5 µM comme valeur critique [Ramsey et al The Oncologist 2018 ;23 :52-61], alors que l'OMEDIT Centre propose 10 µM.

Le bilan des données de méthotrexatémie d'un des Centres obtenues chez près de 300 patients révèle moins de 1% et près de 2% de patients avec une valeur, respectivement, >10µM et >5µM à H48. Il est proposé de réaliser une exploration plus complète en analysant un plus grand nombre de données des Centres du groupe de travail, voire plus largement par le biais du GPCO.

En regroupant ces données, il serait également possible de conduire une analyse selon la méthodologie de pharmacocinétique de population permettant de déterminer les valeurs seuils correspondant aux différents percentiles (par exemple, 5% ou 10% patients les plus exposés). Cette analyse pourrait être complétée de l'analyse des données cliniques, lorsqu'elles sont disponibles : créatininémie, survenue d'une toxicité rénale ou non-rénale… Sans préjuger de la valeur des résultats de l'analyse de ces données rétrospectives, le groupe de travail considère que des données complètes, le plus exhaustives possibles devraient être recueillies de façon prospective pour progresser dans la connaissance de l'efficacité du Voraxaze® et la définition de ces indications. Cela pourrait consister en la mise en place d'un observatoire des pratiques auquel participeraient des centres volontaires (au-delà de ceux constituant le groupe de travail) sur une période déterminée. Seraient relevées les caractéristiques et devenir des patients, traités par Voraxaze® ou non, mais présentant des méthotrexatémies critiques à H24 ou H48, ces deux échéances de méthotrexatémie seraient systématiquement réalisées.

Ces conclusions ont été transmises mi-novembre 2019 à l'ANSM qui a à nouveau sollicité le GPCO pour établir, avant mars 2020, des recommandations à portée nationale en vue d'une prise en charge harmonisée au sein de l'ensemble des établissements français quant aux modalités pratiques d'utilisation du MTX-HD, avec les points non exhaustifs suivants :

- Les durées et vitesses de perfusion
- La surveillance précise de la fonction rénale des patients, avant et après le traitement
- Les modalités d'hydratation et de diurèse alcaline (délai d'initiation, volume, diurèse…)
- La surveillance du pH urinaire et de la diurèse, avant, pendant et après l'administration
- La surveillance de la méthotrexatémie (fréquence de dosage, poursuite de la surveillance…)
- Le sauvetage par l'acide folinique (rappel de la voie d'administration, dose, adaptation de la dose à la surface corporelle ou à la méthotrexatémie…)

Au vu des conclusions du groupe de travail, il apparaît que ces recommandations ne pourront qu'émaner d'une étude observationnelle prospective qui permettra de collecter de manière homogène toutes les données permettant d'évaluer ces différents points. Il a donc été décidé de mettre en place un groupe de travail pour rédiger un protocole d'étude qui sera soumis à l'ANSM.

Si vous souhaitez participer à ce groupe de travail ou si vous avez connaissance de données rétrospectives permettant de répondre à ces questions, merci de prendre contact avec
E. Chatelut (chatelut.etienne@iuct-oncopole.fr)
ou G. Milano (gerard.milano@nice.unicancer.fr)

La revue de presse

Toxicities Associated With Chemotherapy Regimens Containing a Fluoropyrimidine: A Real-Life Evaluation in France

C Barin-Le Guellec, C. Lafay-Chebassier, I. Ingrand, J-F Tournamille, A Boudet, M-C Lanoue, G Defossez, P Ingrand, M-C Perault-Pochat, M-C Etienne-Grimaldi

Aims: Despite fluoropyrimidines (FPs) constituting the main component of the chemotherapy combination protocols in 50% of chemotherapies for solid tumour treatments, incidence data for FP-related toxicity are poorly documented in real life. This study evaluated the number of patients receiving FP-based chemotherapies in France, along with the true incidence of FP-related serious adverse effects (SAEs) before the recent mandatory dihydropyrimidine dehydrogenase (DPD)-screening was introduced by French health authorities, DPD being the rate-limiting enzyme of 5-fluorouracil (5-FU) catabolism.

Methods: Exhaustive data on the number of patients treated with FP-based chemotherapy in 2013-2014 were collected in the Centre-Val de Loire region of France. True incidence of SAEs was extracted from a cohort of 513 patients with incident solid tumours receiving first-line FP-based chemotherapy.

Results: After extrapolation at national level, we estimated that 76,200 patients are currently treated annually with 5FU (53,100 patients, 62% digestive system-related versus 26% breast cancers versus 12% head and neck cancers) or capecitabine (23,100 patients, 45% digestive system-related versus 37% breast cancers versus 18% non-documented). Earlier (in the first two cycles) the SAE incidence rate was 19.3% (95% confidence interval (CI) 16-23%) including one toxic death (0.2%, 95%CI 0-1%). SAE incidence rate was 32.2% (95%CI 28-36%) over the first 6 months of treatment. Incidence of death, life-threatening prognosis or incapacity/disability was 1.4% (95%CI 0.4-2.4%) and 1.6% (95%CI 0.5-2.6%) during first two cycles and first 6 months, respectively.

Conclusion: These data highlight the significant public health issue related to FP toxicity, with around 1200 patients developing FP-related life-threatening prognosis or incapacity/disability annually in France, including 150 toxic deaths. It is hoped that DPD-deficiency screening will reduce such iatrogenic events and eradicate toxic deaths.

Eur J Cancer. 2020 Jan;124:37–46

Is There an Exposure-Response Relationship for Nivolumab in Real-World NSCLC Patients?

A Bellesoeur, E Ollier, M Allard, L Hirsch, P Boudou-Rouquette, J Arrondeau, A Thomas-Schoemann, M Tiako, N Khoudour, J Chapron, F Giraud, M Wislez, D Damotte, A Lupo, M Vidal, J Alexandre, F Goldwasser, M Tod, B Blanchet

Pharmacokinetic/pharmacodynamic data from real-world cohort are sparse in non small-cell lung cancer (NSCLC) patients treated with nivolumab. The aim of this prospective observational study was to explore the exposure-response relationship for effectiveness and toxicity of nivolumab in 81 outpatients with metastatic lung cancer. Nivolumab plasma trough concentrations (Cmin) were assayed at days 14, 28, and 42. Prognostic factors (including Cmin) regarding progression-free survival (PFS) and overall survival (OS) were explored using a multivariate Cox model. A Spearman's rank test was used to investigate the relationship between Cmin and grade >2 immune-related adverse events (irAE). Mean nivolumab Cmin was 16.2 ± 6.0 µg/mL (n = 76), 25.6 ± 10.2 µg/mL (n = 64) and 33.4 ± 11.3 µg/mL (n = 53) at days 14, 28, and 42, respectively. No pharmacokinetic/pharmacodynamic (PK/PD) relationship was observed with either survival or onset of irAE. Multivariable Cox regression analysis identified Eastern Cooperative Oncology Group Performance Status (hazard ratio 1.85, 95%confidence interval 1.02-3.38, p-value = 0.043) and baseline use of corticosteroids (HR 8.08, 95%CI 1.78-36.62, p-value = 0.007) as independent risk factor for PFS and only baseline use of corticosteroids (HR 6.29, 95%CI 1.46-27.08, p-value = 0.013) for OS. No PK/PD relationship for nivolumab was observed in real-world NSCLC patients. This supports the recent use of flat dose regimens without plasma drug monitoring.

Cancers (Basel). 2019 Nov 13;11(11)

Potentiation of Mitotane Action by Rosuvastatin: New Insights for Adrenocortical Carcinoma Management

G Boulate, L Amazit, A Naman, A Seck, A Paci, A Lombes, E Pussard, E Baudin, M Lombes, S Hescot

Mitotane (also termed o,p'-DDD) is the most effective therapy for advanced adrenocortical carcinoma (ACC). Mitotane-induced dyslipidemia is treated with statins. Mitotane and statins are known to exert anti-proliferative effects in vitro; however, the effects of statins have never been directly evaluated in patients with ACC and ACC cells, at least to the best of our knowledge. Thus, in this study, we aimed to examine the effects of the rosuvastatin on ACC cells.

It has been shown that the combined use of mitotane and statins significantly increases the tumor control rate in patients with ACC; however, it would be of interest to elucidate the molecular mechanisms involved in this potentiation. In this study, we examined the effects of mitotane, rosuvastatin and their combination in NCI-H295R human ACC cells using proliferation assays, gene expression analyses and free intracellular cholesterol measurements. The results revealed that mitotane dose-dependently reduced cell viability, induced apoptosis and increased intracellular free cholesterol levels, considered as one of the key features of mitotane action, while rosuvastatin alone reduced cell viability and increased apoptosis at high concentrations. We also demonstrated that rosuvastatin potentiated the effects of mitotane by reducing cell viability, inducing apoptosis, increasing intracellular free cholesterol levels, and by decreasing the expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and ATP binding cassette subfamily a member 1 (ABCA1), genes involved in cholesterol metabolism, and inhibiting steroidogenesis. Collectively, potentiating the effects of mitotane with the use of rosuvastatin may provide novel therapeutic strategies for ACC, given that the combination of these drugs, pending clinical validation, may lead to the better management of ACC.
Int J Oncol. 2019 Jun;54(6):2149–56

Intestinal Bacterial β-Glucuronidase as a Possible Predictive Biomarker of Irinotecan-Induced Diarrhea Severity
A N Chamseddine, M Ducreux, J-P Armand, X Paoletti, T Satar, A Paci, O Mir
Irinotecan is an anticancer drug with a broad spectrum of activity, characterized by multistep and complex pharmacology. Regardless of its schedule of administration, neutropenia and delayed-type diarrhea are the most common side effects. The latter was the dose-limiting toxicity in phase I trials, and its prediction by pharmacogenetic (UGT1A1*28/*28) testing remains sub-optimal. Recent studies have highlighted the important role of the intestinal bacterial β-glucuronidase (BGUS) in the onset of irinotecan-induced diarrhea. Intestinal BGUS hydrolyses glucuronidated metabolites to their toxic form in intestines, resulting in intestinal damage. BGUS selective inhibitors that are currently in development may alleviate irinotecan-induced diarrhea, and may help to reduce its morbidity and enhance its activity. The discussion and description of irinotecan pharmacology may generate ideas that form the basis of clinical trials focusing on a personalized approach to treatment. In addition, we hypothesize that using BGUS activity as a predictive biomarker of irinotecan-induced diarrhea severity will help to select cancer patients for treatment with irinotecan chemotherapy (whether at full or adapted dose).
Pharmacol Ther. 2019;199:1–15

Setting the Dose of Checkpoint Inhibitors: The Role of Clinical Pharmacology
E Chatelut, F Le Louedec, G Milano
Cancer immunotherapy is based on checkpoint inhibitors (CPIs) that significantly improve the clinical outcome of several malignant diseases. These inhibitors are monoclonal antibodies (mAbs) directed at cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), or programmed death-ligand 1 (PD-L1), sharing most of the clinical pharmacokinetic characteristics of mAb targeted therapies, all of which differ from those of cytotoxics and small molecules. Establishing the labeled dose of mAbs, and particularly of the CPIs, represents a true challenge. This review therefore examines the main criteria used for dose selection, along with their limits. The relationships between CPI pharmacokinetic parameters and treatment outcome (efficacy and/or toxicity) differ somewhat among the various drugs, but general features can be identified. Nevertheless, the interpretation of these relationships remains quite controversial. A first interpretation asserts that inter-individual pharmacokinetic variability in clearance has an impact on outcome and should be taken into consideration for dosing individualization. The second considers that higher clearance values observed in some patients result from characteristics associated with poor predictive factors of efficacy. Finally, the schedule, and particularly its frequency of administration, merits rethinking.
Clin Pharmacokinet. 2019 Nov 7 [Online ahead of print]

Clinical Efficacy of the Optimal Biological Dose in Early-Phase Trials of Anti-Cancer Targeted Therapies

P Corbaux, M El-Madani, M Tod, J Péron, D Maillet, J Lopez, G Freyer, B You

Background: Determining the optimal biological dose (OBD) has been described as an alternative strategy to the maximum tolerated doses (MTDs) for identifying the recommended phase II trial doses (RP2Ds) of phase I anti-cancer therapies. However, the clinical relevance is still unknown. An extensive review was performed to assess if the OBDs defined in early-phase trials were useful for subsequent drug development and approvals.

Methods: All the molecular targeted therapies approved by the Food and Drug Administration (FDA) in solid oncology or in haematological malignancies before July 2018 were listed through the National Cancer Institute Database. The early-phase trial publications investigating these drugs as single agents were retrieved and analysed to identify the drugs for which OBDs were reported. The publications of subsequent pivotal efficacy clinical trials leading to the approvals were retrieved, and OBDs compared with the final labelled doses and dosing schedules.

Results: A total of 87 early-phase trial publications were analysed, corresponding to 81 FDA-approved targeted therapies. OBDs were reported for 40% (32/81) of these drugs (19 small molecules, 13 monoclonal antibodies). MTDs were not identified for 59% (19/32) of molecules. When the OBDs were selected as the RP2Ds (18/32 molecules), the final FDA-approved doses were consistent with the OBDs for 83% of the drugs, which is much higher than the previously reported 58% rate when MTDs were chosen as the RP2Ds.

Conclusion: Although still poorly investigated, the OBD may be a relevant and complementary end-point for early-phase trials of targeted therapies.

Eur J Cancer. 2019 Oct;120:40–6

Prodrugs as Drug Delivery System in Oncology

J Delahousse, C Skarbek, A Paci

The use of conventional chemotherapy in the treatment of cancer has been restricted by the lack of cell specificity, which causes toxicity regarding healthy cells resulting in limiting side effects responsible for low therapeutic efficiency. To overcome these drawbacks, the design of prodrugs has evolved and improved by covalently linking the drug through a degradable spacer.

The use of these prodrugs as drug delivery systems, which are able to inactivate the drug during its biodistribution to specifically deliver the drug to its target, is an important breakthrough in cancer therapy. This strategy consisting in the covalent binding of a promoiety to daily used therapeutic compounds has been clinically proven in the design of targeted prodrugs leading enhanced therapeutic efficacy and increase of the therapeutic index. This review summarizes and compares several strategies that improve the therapeutic index of chemotherapy (i.e. conventional drugs) by their chemical transformation into prodrugs improving pharmacokinetic profiles and optimizing administration routes in comparison to the initial drug. This review provides an overview of the methods used to control the structure and function of prodrugs and, ultimately, their current and future potential in increasing the therapeutic index of daily used anticancer drugs. First, prodrugs' design and their activation within the tumor microenvironment or within the tumor cell will be exposed. Then, the different strategies used leading to these prodrugs will be presented.

Cancer Chemother Pharmacol. 2019 Nov;84(5):937–58

Antidrug Antibodies Against Immune Checkpoint Blockers: Impairment of Drug Efficacy or Indication of Immune Activation?

D Enrico, A Paci, N Chaput, E Karamouza, B Besse

The generation of antibodies following exposure to therapeutic drugs has been widely studied, however in oncology, data in relation to their clinical relevance are limited. Antidrug antibodies (ADAs) can cause a decrease in the amount of drug available, resulting in some cases in decreased antitumor activity and a consequent impact on clinical outcomes. Several immunologic factors can influence the development of ADAs, and in addition, the sensitivity of the different testing methods used in different studies can vary, representing an additional potential confounding factor. The reported frequency of ADA-positive patients following treatment with immune checkpoint inhibitors varies from as low as 1.5% for pembrolizumab to 54% for atezolizumab. This latter drug is the only immune checkpoint inhibitor to have undergone an expanded analysis of the clinical implications of ADAs, but with discordant results. Given that immune checkpoint inhibitors can modify the immune response and potentially impact ADA formation, data from published as well as prospective trials need to be evaluated for a better understanding of the clinical implications of ADAs in this setting.

Clin Cancer Res. 2019 Nov 22 [Epub ahead of print]

Crizotinib-induced Immunogenic Cell Death in Non-Small Cell Lung Cancer

P Liu, L Zhao, J Pol, S Levesque, A Petrazzuolo, C Pfirschke, C Engblom, S Rickelt, T Yamazaki, K Iribarren, L Senovilla, L Bezu, E Vacchelli, V Sica, A Melis, T Martin, L Xia, H Yang, Q Li, J Chen, S Durand, F Aprahamian, D Lefevre, S Broutin, A Paci, A Bongers, V Minard-Colin, E Tartour, L Zitvogel, L Apetoh, Y Ma, M J Pittet, O Kepp, G Kroemer

Immunogenic cell death (ICD) converts dying cancer cells into a therapeutic vaccine and stimulates antitumor immune responses. Here we unravel the results of an unbiased screen identifying high-dose (10 µM) crizotinib as an ICD-inducing tyrosine kinase inhibitor that has exceptional antineoplastic activity when combined with non-ICD inducing chemotherapeutics like cisplatin. The combination of cisplatin and high-dose crizotinib induces ICD in non-small cell lung carcinoma (NSCLC) cells and effectively controls the growth of distinct (transplantable, carcinogen- or oncogene induced) orthotopic NSCLC models. These anticancer effects are linked to increased T lymphocyte infiltration and are abolished by T cell depletion or interferon-γ neutralization. Crizotinib plus cisplatin leads to an increase in the expression of PD-1 and PD-L1 in tumors, coupled to a strong sensitization of NSCLC to immunotherapy with PD-1 antibodies. Hence, a sequential combination treatment consisting in conventional chemotherapy together with crizotinib, followed by immune checkpoint blockade may be active against NSCLC.

Nat Commun. 2019 02;10(1):1486

Identifying the Reactive Metabolites of Tyrosine Kinase Inhibitors in a Comprehensive Approach: Implications for Drug-Drug Interactions and Hepatotoxicity

M-N Paludetto, F Puisset, E Chatelut, C Arellano

Tyrosine kinase inhibitors (TKI) are small heterocyclic molecules targeting transmembrane and cytoplasmic tyrosine kinases that have met with considerable success in clinical oncology. TKI are associated with toxicities including liver injury that may be serious and even life-threatening. Many of them require warnings in drug labeling against liver injury, and five of them have Black Box Warning (BBW) labels. Although drug-induced liver injury is a matter of clinical and industrial concern, little is known about the underlying mechanisms that likely involve reactive metabolites (RM). RM are electrophiles or radicals originating from the metabolic activation of particular functional groups, known as structural alerts or toxicophores. RM are able to covalently bind to proteins and macromolecules, causing cellular damage and even cell death. If the adducted protein is the enzyme involved in RM formation, time-dependent inhibition of the enzyme-also called mechanism-based inhibition (MBI) or inactivation-can occur and lead to pharmacokinetic drug-drug interactions. To mitigate RM liabilities, common practice in drug development includes avoiding structural alerts and assessing RM formation via RM trapping screens with soft and hard nucleophiles (glutathione, potassium cyanide, and methoxylamine) in liver microsomes. RM-positive derivatives are further optimized to afford drug candidates with blocked or minimized bioactivation potential. However, different structural alerts are still commonly used scaffolds in drug design, including in TKI structures. This review focuses on the current state of knowledge of the relations among TKI structures, bioactivation pathways, RM characterization, and hepatotoxicity and cytochrome P450 MBI in vitro.

Med Res Rev. 2019 Nov;39(6):2105–52

Involvement of Pazopanib and Sunitinib Aldehyde Reactive Metabolites in Toxicity and Drug–Drug Interactions in Vitro and in Patient Samples

M-N Paludetto, J-L Stigliani, A Robert, V Bernardes-Génisson, E Chatelut, F Puisset, C Arellano

Tyrosine kinase inhibitors (TKI) are targeted anticancer drugs that have been successfully developed over the past 2 decades. To date, many of them (around 70%) require warnings for liver injury and five of them, including pazopanib and sunitinib, have Black Box Warning (BBW) labels. Although TKI-induced hepatotoxicity is the first cause of drug failures in clinical trials, BBW labels, and market withdrawals, the underlying mechanisms remain unclear. However, the recent discovery of new reactive metabolites (RM) with aldehyde structures during pazopanib and sunitinib metabolism offers new perspectives for investigating their involvement in the toxicity of these two TKI. These hard electrophiles have a high reactivity potential toward proteins and are thought to be responsible for cytochrome P450 inactivation, drug–drug interactions (DDI), and liver toxicity. We report here, for the first time, the presence of these aldehyde RM in human plasma samples obtained during drug monitoring.

Docking experiments in the CYP3A4 active site were performed and showed that pazopanib and sunitinib fitting in the catalytic site are in accordance with their regioselective oxidation to aldehydes. They also suggested that aldehyde RM may react with lysine and arginine residues. Based on these results, we studied the reactivity of the aldehyde RM toward lysine and arginine residues as potential targets on the protein framework to better understand how these RM could be involved in liver toxicity and drug–drug interactions. Adduct formation with different hepatic and plasma proteins was investigated by LC-MS/MS, and adducts between pazopanib or sunitinib aldehyde derivatives and lysine residues on both CYP3A4 and plasma proteins were indeed shown for the first time.
Chem Res Toxicol. 2019 Sep 26 [Epub ahead of print]

Impact of Interleukin-6 on Drug-Metabolizing Enzymes and Transporters in Intestinal Cells
F Simon, J Garcia, L Guyot, J Guitton, G Vilchez, C Bardel, M Chenel, M Tod, L Payen
Inflammatory response is characterized by an increase of several cytokines. Some are known to modify drugs pharmacokinetic by reducing the expression levels of drug-metabolizing enzymes (DMEs) and transporters. This impact of inflammatory signaling is well established in hepatic cells, but not in intestinal cells. EpiIntestinal is a 3D human small intestinal tissue model with epithelial polarity, allowing good evaluation of metabolism and drug transport. This study aimed to analyze the effect of IL-6 on this tissue model. RNA sequencing was performed in cells incubated with 5, 10, or 20 ng/mL IL-6 for 8 h to 72 h to study the impact of IL-6 on drug metabolism and pharmacokinetics gene expression. The influence of IL-6 on the activity of cytochromes P450 (CYPs) was studied by measuring metabolite formation of specific substrates with LC-HRMS. Its impact on ATP-binding cassette (ABC) transport was evaluated by measuring intra- and extracellular substrates using spectrofluorometry. Exposure of EpiIntestinal cells to IL-6 resulted in reduction of some CYP mRNAs, such as CYP2C19, CYP2C9, and CYP3A4, by 40% to 50%. Activities of these CYPs were also decreased in EpiIntestinal cells by 20% to > 75%. IL-6 exposure did not modify ABCB1 and ABCCs transporter activities in this model. This study shows that gene expression levels and activities of drug-metabolizing enzymes and ABC transporters may be altered by the pro-inflammatory cytokine IL-6 in intestinal cells. If these results are confirmed in vivo, it may result in pharmacokinetic modifications, such as pre-systemic metabolism, with clinical effects, and require dosage adaptation.
AAPS J. 2019 Dec 20;22(1):16

Quantitative Prediction of Interactions Mediated by Transporters and Cytochromes: Application to Organic Anion Transporting Polypeptides, Breast Cancer Resistance Protein and Cytochrome 2C8
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Background: The in vivo mechanistic static model (IMSM) is an effective method to predict the magnitude of drug-drug interactions (DDIs) mediated by cytochromes.
Objective: The aim of this study was to extend the IMSM paradigm to DDIs mediated by organic anion transporting polypeptide (OATP) 1Bs, breast cancer resistance protein (BCRP) and cytochrome 2C8.
Methods: First, a generic model for this kind of interaction was established, and a literature search was then conducted to retrieve the area under the concentration-time curve (AUC) ratio of a large set of DDIs involving OATP1B1, OATP1B3, BCRP and cytochromes 2C8 or 3A4. The model was fitted to the data to estimate the characteristic parameters (contribution ratios [CRs] and inhibition or induction potencies [IXs]) by nonlinear regression, and the model was qualified by external validation on a different dataset. Lastly, the model was used to identify the risks of overexposure by DDIs of this type.
Results: A total of 27 substrates, 26 inhibitors, 3 inducers and 3 genetic variants were considered in the regression analysis. The number of observations (AUC ratios, denoted as Robs) was 101. Forty-six CRs and 47 IXs were estimated. The proportions of predictions within 0.67- to 1.5-fold and 0.5- to twofold Robs were 90% and 99%, respectively, for the internal validation, and 78% and 96%, respectively, for the external validation. The median fold-error was 1.03 (the ideal value is 1). The interquartile range of fold-error was 0.31, and the relative standard error of parameter estimates was, at most, 17%.
Conclusions: The IMSM approach was successfully extended to DDIs mediated by OATP1Bs, BCRP and cytochromes 2C8 or 3A4. The method revealed good predictive performances by internal and external validation.
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FUSAFE individual patient data meta-analysis to assess the performance of dihydropyrimidine dehydrogenase gene polymorphisms for predicting grade 4-5 fluoropyrimidine toxicity

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Background: Despite decades of research, performance of DPYD genotyping to predict FP toxicity (tox) is poorly documented. GPCO-UNICANCER and RNPGx groups initiated the FUSAFE MA on individual patient data (IPD) to assess the prognostic value of consensual deleterious DPYD variants on grade (G) 4-5 FP tox.

Methods: Eligibility criteria included unbiased recruitment of Caucasian patients (pts) without FP dose adjustment based on DPD status. Main endpoint was 12 weeks hematological or digestive G4-5 tox. Age, sex, body mass index (BMI), advanced stage (M- vs Mþ), FP drug (5FU vs capecitabine), FP administration (bolus6continuous vs continuous alone or p.o.) and associated anticancer drugs (AAD) were collected. Multivariable logistic models were applied. Performance was assessed by AUC and diagnostic indices maximizing Youden index.

Results: From the 18 identified eligible studies(10230 pts), 14 were included (9030 pts), with complete IPD collected for 6403 pts (84% colorectal, 16% Mþ, 66% 5FU, 80% AAD). G4-5 tox prevalence was 8% (518 events). DPYD variants *2A, D949V, *13 and HapB3 were carried by 0.9%, 1.2%, 0.2% and 3.9% of pts, respectively. The clinical model (M1) retained age, sex, BMI, FP-administration,AAD. Adding variants *2A/D949V/*13 (at least one mutated allele) significantly (p<.0001) improved the model (M2). Further adding HapB3 did not improve the model (p¼.24, M3). M3-adjusted OR (95%CI) was 10.0 (6.9- 14.7) for the 3 variants *2A/D949V/*13 and 2.1 (1.4-3.0) for HapB3. Similar results were observed on colorectal pts only, or when excluding bolus administration alone.

Conclusions: This is the largest MA on DPYD genotyping and toxicity. It shows the relevance of clinical variables and of the 3 consensual DPYD variants. Despite its association with tox, HapB3 does not improve the discriminant ability to identify pts at risk of G4-5 toxicity.

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