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Clinical implications of food–drug interactions with small-molecule kinase inhibitors

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During the past two decades, small-molecule kinase inhibitors have proven to be valuable in the treatment of solid and haematological tumours. However, because of their oral administration, the intrapatient and interpatient exposure to small-molecule kinase inhibitors (SMKIs) is highly variable and is affected by many factors, such as concomitant use of food and herbs. Food–drug interactions are capable of altering the systemic bioavailability and pharmacokinetics of these drugs. The most important mechanisms underlying food–drug interactions are gastrointestinal drug absorption and hepatic metabolism through cytochrome P450 isoenzymes. As food–drug interactions can lead to therapy failure or severe toxicity, knowledge of these interactions is essential. This Review provides a comprehensive overview of published studies involving food–drug interactions and herb–drug interactions for all registered SMKIs up to Oct 1, 2019. We critically discuss US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines concerning food-drug interactions and offer clear recommendations for their management in clinical practice.

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Introduction

Since the start of this millennium, a new class of anticancer drugs has gained an important role in the treatment of solid and haematological tumours: the small-molecule kinase inhibitors (SMKIs). SMKIs cause cell-cycle arrest, induce apoptosis, inhibit angiogenesis, and modulate tumour immunity by specifically inhibiting cellular signal transduction through blocking dysregulated protein kinases.[1] Some SMKIs are registered for specific oncogenic driver mutations, which need to be determined using molecular diagnostics. As a result, this tailored treatment approach often results in better efficacy with a favourable risk-benefit balance when compared with chemotherapy.[2,3]

With the introduction of SMKIs, new challenges have emerged. Different from most chemotherapeutic drugs, which are administered intravenously, SMKIs are administered orally. Although oral intake improves patient comfort and flexibility of treatment (eg, place and timing of intake), the variability in intrapatient and interpatient exposure to SMKIs is high[4] and is affected by many factors, such as drug-drug interactions, concomitant use of food and medicinal herbs, genetic variance, and lifestyle.[5] The effect of food on drug exposure could be clinically significant. For example, administration of lapatinib, combined with a high-fat meal, increases its plasma concentrations more than three times.[6] Besides a concomitant meal, other specific foods and beverages might cause food–drug interactions (FDIs). Additionally, some herbal products that are frequently used by patients with cancer have substantial potency to cause herb–drug interactions (HDIs).[7] FDIs and HDIs can affect plasma drug concentration, which is a result of the absorption, distribution, metabolism, and elimination of a drug (ie, pharmacokinetic interactions). Most patients and clinicians are insufficiently aware of possible FDIs and HDIs and their potential risk for treatment inefficacy or toxicity.[8] Hence, it is crucial to have thorough knowledge of these FDIs and HDIs for safe and optimal treatment of patients with cancer.

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provide recommendations for assessing possible FDIs, to ensure optimal dose finding and drug labelling.[2,3] To define whether or not food intake clinically relevantly affects the plasma concentration of a drug, the FDA applies the bioequivalence range of 80–125% for the 90% CI of total exposure—known as the area under the curve (AUC)—or maximal plasma concentration (C_{max}). SMKI administration during the fasting state serves as the reference.[3] Regarding herbs, only EMA states that efforts should be made to investigate a possible HDI when reports suggest a clinically relevant interaction.[2]

This Review presents a comprehensive overview of published studies regarding FDIs and HDIs for all registered SMKIs (until Oct 1, 2019). It discusses the most important mechanisms underlying FDIs and HDIs and aims to provide clear recommendations to manage clinically relevant interactions in daily practice.

Absorption

Gastrointestinal absorption has a key role in the plasma concentrations of SMKIs. Before entering the portal bloodstream, drugs must first dissolve and pass enterocyte cell membranes. The solubility of weakly basic drugs, such as SMKIs, is largely dependent on the intragastric pH. The intragastric pH is increased by food, acid-suppressing drugs, or both.[9] Postprandial rise in intragastric pH shifts the drug's ionised/non-ionised equilibrium to the non-ionised form, and reduces SMKI solubility and absorption. Since most SMKIs are also lipophilic drugs,[10] they probably dissolve better when administered concomitantly with a (fat) meal. Additionally, food enhances splanchnic blood flow and bile secretion and it increases intragastric and intestinal retention and transit time,[11] thus increasing drug absorption potential.

Besides passive diffusion, multiple drug transporters are important for drug permeability. Organic anion and cation (uptake) peptides actively transport the SMKI into

the enterocyte from which the drug is transported (or can diffuse) to the portal vein. Contemporaneous counter (efflux) transport to the intestinal lumen can occur by P-glycoprotein (ATP-binding cassette B1; ABCB1) and breast cancer resistance protein (BCRP; ABCG2).[5] In case of high-passive diffusion, food interactions with transporters are not likely to result in clinically significant altered exposures. Various food constituents (eg, curcumin, flavonoids, bitter melon) and beverages (eg, tea catechins) are known to inhibit P-glycoprotein, whereas St John's wort is a potent P-glycoprotein inducer, which could decrease drug exposure.[12]

Food–drug interactions

High-fat meal

High-fat test meals consist of 800–1000 kcal of which approximately 500–600 kcal is derived from fat and 250 kcal from carbohydrates (eg, a full English breakfast).[2,3] Concomitant SMKI administration with a high-fat meal resulted in a clinically significant increase of C_{max} and AUC for twelve SMKIs, and in a 29–51% decrease of C_{max} and AUC for three SMKIs (ie, afatinib, dabrafenib, and sorafenib). We noted the relative changes in the C_{max} and AUC when an SMKI at its therapeutic dose is administered with a high-fat, moderate-fat, or low-fat meal, compared with the fasted state (table 1).[2,3,6,10,13–45] On the contrary, for seventeen SMKIs, concomitant food intake showed no relevant effect on its AUC. However, brigatinib, encorafenib, ruxolitinib, tivozanib, and trametinib had decreases in C_{max} of 20% or more with a high-fat meal, but had no effect on their AUC.

Moderate-fat and low-fat meals

Moderate-fat test meals contain half the caloric content of a high-fat meal, with fat contributing to approximately 150 kcal.[2] Low-fat test meals are less consistent between studies because they are neither defined by FDA nor EMA,[2,3] but these meals roughly consist of less than 100 kcal derived from fat (eg, a continental breakfast). Similar to high-fat meals, concomitant SMKI administration with moderate-fat meals did not result in clinically significant FDIs for axitinib and sorafenib. The absence of clinically relevant FDIs also applies to the low-fat meals that were studied for eight SMKIs. On one hand, only when FDIs with a high-fat meal are known to occur, further investigation of drug intake with other types of meals (eg, moderate-fat or low-fat meals) is indicated to improve patient comfort, or to reduce drug dosage and costs. On the other hand, when FDIs do not occur with high-fat diets, doing additional FDI studies with lower fat meals is not indicated, because a high-fat meal functions for lipophilic drugs as proof-of-principle with maximal interacting potential.

General recommendations

Alteration of C_{max} or AUC caused by an FDI could potentially alter the drugs' toxicity and effectiveness. Recommendations on food intake should be based on combining optimal effectiveness with the lowest toxicity possible. In general, these recommendations are straightforward: when food greatly decreases an SMKI's exposure, patients should be instructed to take the SMKI without food, because it could decrease the effectiveness of the drug. When food does not affect an SMKI's AUC, patients should be given free choice whether to use the SMKI with or without food. However, when food substantially increases a SMKI's exposure without affecting its tolerability, more balanced recommendations should be given. Only when safety has been confirmed, SMKIs with FDIs that increase the exposure are allowed to be administered with food. For several SMKIs, viable or promising correlations have been reported between pharmacokinetic parameters (eg, AUC or plasma trough concentration) and survival or response.[46] In such a case, the optimal method to individualise SMKI treatment is the frequent monitoring of SMKI plasma concentrations, also known as therapeutic drug monitoring.[47] When plasma concentrations decrease to less than the therapeutic threshold, despite a good adherence, patients might be advised to take the SMKI concomitantly with a meal.

Specific recommendations

We noted the relative changes in C_{max} and AUC of all SMKIs when taken with a high-fat meal (figure 1). FDA and EMA recommendations are expected to be strict: SMKIs shown in the grey area can be taken with or without food, whereas SMKIs outside the grey area can only be taken without food (ie, fasted). However, for some SMKIs, FDA and EMA recommendations are not in accordance with these principles.

Gefitinib, ibrutinib, and vemurafenib

Gefitinib, ibrutinib, and vemurafenib are known for having a clinically significant food effect, but nonetheless they are recommended by FDA and EMA to be administered with or without food (table 1). Especially for vemurafenib, in which a high-fat meal increases its C_{max} by 150% and AUC by 400%,[43] this recommendation is remarkable. Considering vemurafenib's plasma concentration to be associated with overall survival and developing common terminology criteria for adverse events (CTCAE) grade of 2 or higher skin rash,[48] it is important to reach an effective exposure with minimal toxicity. With the current recommendation, 14% of treated patients do not reach plasma trough concentrations.[48] As vemurafenib has a substantial FDI, and interpatient variability is decreased with food by 49%,[43] we recommend vemurafenib to be taken with food. Awareness and counselling for possible skin rash (CTCAE grade ≥2) are also important. Furthermore, therapeutic drug monitoring could be used to establish drug concentrations at therapeutic levels in the fasted state. For ibrutinib, there is no conclusive evidence for an

	Change in C_{max} (%)	Change in AUC (%)	Importance	FDA or EMA recommendation	Author recommendation
Afatinib[2,3,13]					
High-fat meal	–50%	–39%	Moderate	Take without food	Take without food
Alectinib[2,14]					
High-fat meal	170%	192% to 210%	Major	Take with food	Take with food*
Axitinib[2,3,15]					
High-fat meal	11%	19%	Minor	Take with or without food	Take with or without food
Moderate-fat meal	–16%	–10%	Minor	Take with or without food	Take with or without food
Binimetinib[2,3]					
High-fat meal	–17%	–1%	Minor	Take with or without food	Take with or without food
Low-fat meal	–29%	No effect	Minor	Take with or without food	Take with or without food
Bosutinib[2,3,16]					
High-fat meal	42% to 80%	54% to 70%	Major	Take with food	Take with food
Brigatinib[2,3,45]					
High-fat meal	–24% to –13%	–2%	Minor	Take with or without food	Take with or without food
Cabozantinib[2,3,17]					
High-fat meal	41%	57%	Moderate	Take without food	Take without food
Ceritinib[2,3,18,19]					
High-fat meal	41%	73%	Major	Take 450 mg with food or 750 mg without food	Take preferably 450 mg with food, or 750 mg without food
Low-fat meal	43% to 45%	54% to 58%	Moderate	Take 450 mg with food or 750 mg without food	Take preferably 450 mg with food, or 750 mg without food
Low-fat meal (450 mg dose) versus fasted (750 mg dose)	3%	4%	Minor	Take 450 mg with food or 750 mg without food	Take preferably 450 mg with food, or 750 mg without food
Low-fat meal (600 mg dose) versus fasted (750 mg dose)	25%	24%	Moderate	Take 450 mg with food or 750 mg without food	Take preferably 450 mg with food, or 750 mg without food
Cobimetinib[2,3,20]					
High-fat meal	0% to 7%	0% to 10%	Minor	Take with or without food	Take with or without food
Crizotinib[2,3,21,22]					
High-fat meal	–14% to 0%	–14% to 0%	Minor	Take with or without food	Take with or without food
Dabrafenib[2,3,23]					
High-fat	–51%	–31%	Moderate	Take without food	Take without food
Dasatinib[2,3]					
High-fat meal	NA	14%	Minor	Take with or without food	Take with or without food
Low-fat meal	NA	21%	Minor	Take with or without food	Take with or without food
Encorafenib[2,3]					
High-fat meal	–36%	–4% to 0%	Minor	Take with or without food	Take with or without food
Erlotinib[24,25]					
High-fat meal	33% to 56%	33% to 66%	Moderate	Take without food	Take without food
Gefitinib[2,26]					
High-fat meal	32%	37%	Moderate	Take with or without food	Take with or without food
Ibrutinib[2,3,27,28]					
High-fat meal	163% to 400%	62% to 200%	Major	Take with or without food	Take with food
Imatinib[2,29]					
High-fat meal	–15% to –11%	–7%	Minor	Take with food	Take with or without food
Lapatinib[2,3,6,30]					
High-fat meal	166% to 203%	100% to 325%	Major	Take without food	Take with a low-fat meal
Low-fat meal	90% to 150%	80% to 200%	Major	Take without food	Take with a low-fat meal
Lenvatinib[2,3,31,32]					
High-fat meal	–4% to 0%	0% to +6%	Minor	Take with or without food	Take with or without food
Nilotinib[2,3,33]					
High-fat meal	48% to 112%	43% to 82%	Major	Take without food	Take without food
Low-fat meal	33% to 55%	15% to 29%	Moderate	Take without food	Take without food

(Table 1 continues on next page)

	Change in C_{max} (%)	Change in AUC (%)	Importance	FDA or EMA recommendation	Author recommendation
(Continued from previous page)					
Nintedanib[2,3]					
High-fat meal	19%	21%	Minor	Take with food	Take with or without food
Osimertinib[2,3,34,35]					
High-fat meal	–7% to 14%	6% to 19%	Minor	Take with or without food	Take with or without food
Pazopanib[2,3,36,44]					
High-fat meal	108%	134%	Major	Take without food	Take preferably 600 mg with food, or 800 mg without food
Low-fat meal	110%	92%	Major	Take without food	Take preferably 600 mg with food, or 800 mg without food
Low-fat meal (600 mg dose) versus fasted (800 mg dose)	12%	9%	Minor	Take without food	Take preferably 600 mg with food, or 800 mg without food
Ponatinib[2,3,37]					
High-fat meal	–6% to 0%	0% to 10%	Minor	Take with or without food	Take with or without food
Low-fat meal	–6 % to 0%	–2% to 0%	Minor	Take with or without food	Take with or without food
Regorafenib[2,3]					
High-fat meal	73%	48%	Moderate	Take with food or low-fat meal	Take without food
Low-fat meal	54%	36%	Moderate	Take with food or low-fat meal	Take without food
Ruxolitinib[2,3,38]					
High-fat meal	–24%	5%	Minor	Take with or without food	Take with or without food
Sorafenib[2,3]					
High-fat meal	NA	–30% to –29%	Moderate	Take without food	Take without food
Moderate-fat meal	NA	no effect	Minor	Take without food	Take without food
Sunitinib[2,3,39]					
High-fat meal	0% to 4%	0% to 12%	Minor	Take with or without food	Take with or without food
Tivozanib[2,3,40]					
High-fat meal	–23%	7%	Minor	Take with or without food	Take with or without food
Trametinib[2,3,41]					
High-fat meal	–70%	–10%	Minor	Take without food	Take with or without food
Vandetanib[3,42]					
High-fat meal	–11% to 17%	0% to 10%	Minor	Take with or without food	Take with or without food
Vemurafenib[2,3,43]					
High-fat meal	114% to 150%	150% to 400%	Major	Take with or without food	Take with food

The recommendation for all SMKIs is to reduce dose if intolerable toxic effects occur. Importance of the food-drug interaction is considered minor (not clinically relevant) when AUC is <20% decreased or <25% increased, moderate when AUC is ≥20% and <50% decreased or ≥25% and <67% increased, and major when AUC is ≥67% increased or ≥50% decreased. C_{max}=maximal plasma concentration. AUC=area under the curve. SMKI=small-molecule kinase inhibitors. *As alternative for dose reduction, consider administration without food if intolerable toxic effects occur.

Table 1: **Overview of the relative changes in the C_{max} and AUC when an SMKI at its therapeutic dose is administered with a high-fat, moderate-fat, or low-fat meals, compared with the fasted state**

exposure–toxicity relationship,[3,27,28] albeit complete target receptor occupation (and possibly response) is exposure dependent.[49] Therefore, we advise ibrutinib to be taken with food. Gefitinib has the most moderate FDI (32% increase in C_{max} and 37% increase in AUC),[26] which might be the reason for its liberal food recommendation (ie, administration irrespective of food intake).

Alectinib, bosutinib, and regorafenib

Although alectinib, bosutinib, and regorafenib are affected by FDIs, they are specifically recommended to be administered with food. The registration study of alectinib was done with concomitant food administration[50] and no differences in side-effects with fasted conditions were found,[14] therefore patients should be instructed to take alectinib with food. Furthermore, bosutinib was shown to be better tolerated with food at therapeutic doses because the incidence of gastrointestinal adverse events decreased when bosutinib was taken with food.[16] EMA's rationale to recommend administration concomitant with a low-fat meal is based on a better exposure to regorafenib's active metabolites.[2] However, no toxicity data of these studies are reported.[2,3] Hence, we cannot endorse the recommendation of both FDA and EMA to take regorafenib with a (light)

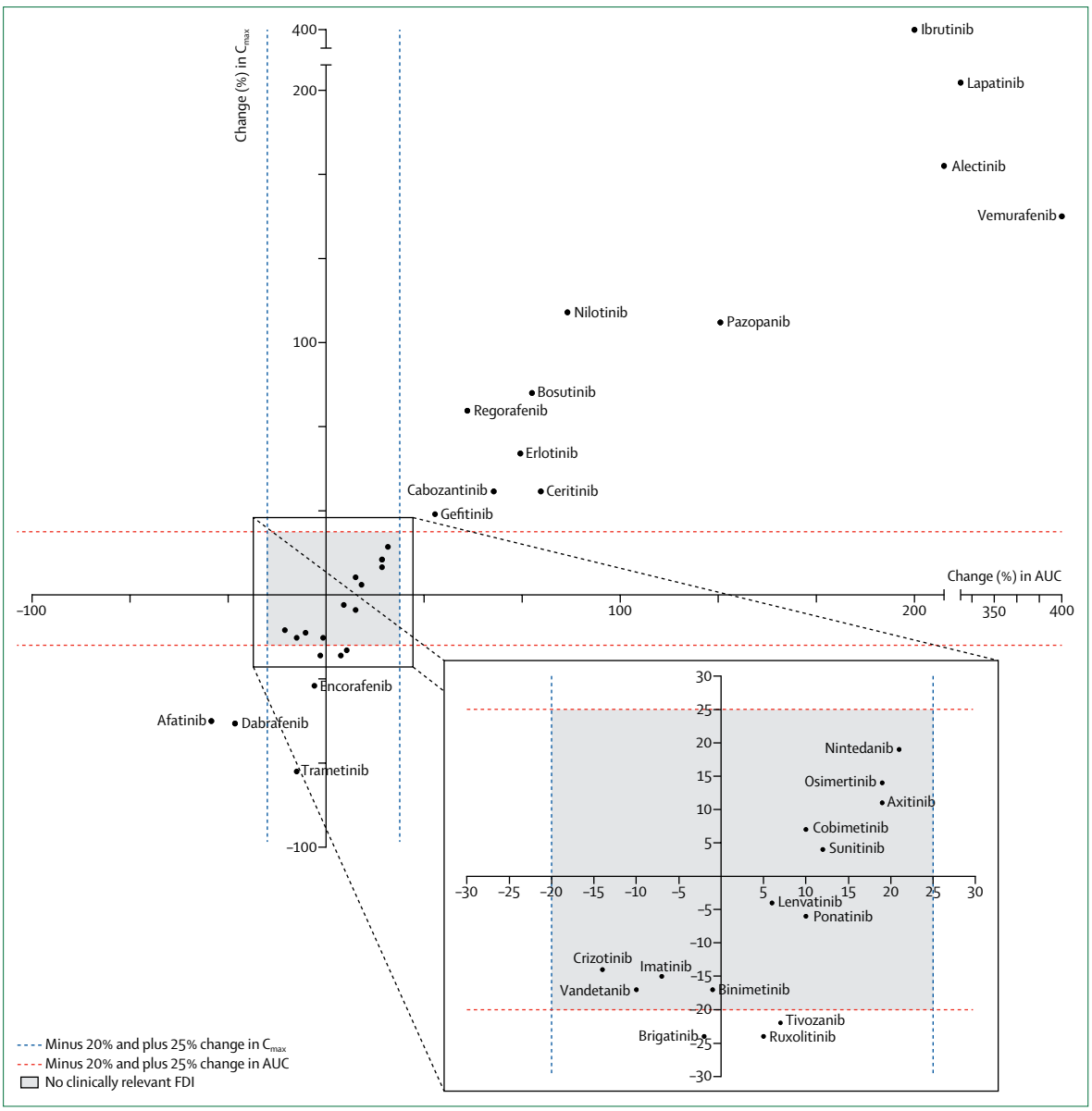

Figure 1: **Relative change in AUC and C_{max} of SMKIs administered with a high-fat meal**
Data derived from table 1. The central grey area emphasises the range of 80% to 125% in which no clinically relevant FDI occurs. Dabrafenib and sorafenib are not displayed because of unavailable C_{max} data. AUC=area under the curve. C_{max}=maximal concentration. SMKIs=small-molecule kinase inhibitors. FDI=food–drug interaction.

meal.[2,3] Theoretically, when drug absorption and systemic exposure is increased, the residual gastrointestinal drug fraction with accompanied gastrointestinal toxicity is reduced. For SMKIs, tolerability depends more on local than systemic adverse events, therefore an FDI could optimise efficacy and decrease toxicity simultaneously.[16]

Imatinib, nintedanib, and trametinib

In line with this assumption, imatinib and nintedanib are recommended to be taken concomitantly with food, even though absorption is not clinically affected by food consumption. For both SMKIs toxicity data are lacking. We suggest a recommendation based on patient's preference—ie, intake with or without food. However, even though food does not affect trametinib's AUC, FDA and EMA recommend taking trametinib without food. This recommendation is based on extrapolated calculations by Cox and colleagues,[41] who studied the single-dose pharmacokinetics of trametinib. In our opinion, both single-dose pharmacokinetic studies and pharmacokinetic modelling studies do not adequately show the in-vivo impact of an FDI. Consistently, because trametinib does not have an FDI, trametinib can be administered irrespective of food consumption.

	Change in C_{max} variability (%)	Change in AUC variability (%)	Change in T_{max} (%; fed T_{max})
Afatinib[2,3,13]			
High-fat meal	+63%	+2%	+130% (6·9 h)
Alectinib[2,14]			
High-fat meal	–20%	–6%	+100% (4 h)
Axitinib[2,3,15]			
High-fat meal	–45%	–9%	+50% (3 h)
Moderate-fat meal	–34%	+9%	+40% (2·8 h)
Binimetinib[2,3]			
High-fat meal	–56%	–33%	+132% (2 h)
Low-fat meal	–50%	–8%	+43% (1·3 h)
Bosutinib[2,3,16]			
High-fat meal	–61%	–70%	+100% (6 h)
Brigatinib[2,3,45]			
High-fat meal	–31%	–11%	+250% (5 h)
Cabozantinib[2,3,17]			
High-fat meal	–5%	+4%	+50% (6 h)
Ceritinib[2,3,18,19]			
High-fat meal	–32%	–24%	+25% (10 h)
Low-fat meal	–55% to –44%	–49% to –46%	–12% to +33% (7 to 8 h)
Low-fat meal (450 mg dose) versus fasted (750 mg dose)	NA	NA	+2% (6 h)
Low-fat 600 mg versus fasted 750 mg	NA	NA	+2% (6 h)
Cobimetinib[2,3,20]			
High-fat meal	+29%	+22%	+300% (6 h)
Crizotinib[2,3,21,22]			
High-fat meal	+12%	+8%	No effect (5 h)
Dabrafenib[2,3,23]			
High-fat meal	–11%	–12%	+200% (6 h)
Dasatinib[2,3]			
High-fat meal	NA	NA	NA
Low-fat meal	NA	NA	NA
Encorafenib[2,3]			
High-fat meal	+37%	–9%	+130% (3·5 h)
Erlotinib[24,25]			
High-fat	–51% to +9%	–38% to +25%	+39% to 74% (3·9 to 4·2 h)
Gefitinib[2,26]			
High-fat meal	–21%	–3%	No effect (5 h)
Ibrutinib[2,3,27,28]			
High-fat meal	–63% to +2%	–18% to +2%	–53% to +167% (1·5 to 4 h)
Imatinib[2,29]			
High-fat meal	–20%	–37%	+37% (3·7 h)
Lapatinib[2,3,6,30]			
High-fat meal	No effect	–20%	+50% to 67% (5 to 6 h)
Low-fat meal	–16%	–13%	0% to 30% (3·9 to 4 h)
Lenvatinib[2,3,31,32]			
High-fat meal	–52%	–24%	+100% to 150% (4 to 5 h)
Nilotinib[2,3,33]			
High-fat meal	–16% to –13%	–14% to +25%	+20% to 25% (3 to 5 h)
Low-fat meal	–5% to +16%	+7% to 43%	No effect (4 h)

(Table 2 continues on next page)

Lapatinib

A multiple-dose FDI study with lapatinib showed a major FDI with no unexpected toxicity when it was taken 1 h after high-fat food consumption.[30] This effect is similar to administration concomitant with a low-fat meal.[6] Extrapolating these results, we recommend lapatinib intake with a low-fat meal. That would additionally allow lapatinib to be co-administered with capecitabine, when given as combination treatment for HER2-positive breast cancer.[2,3]

Ceritinib and pazopanib

The exposure to ceritinib and pazopanib is greatly affected by FDIs. However, multiple-dose FDI studies compared exposure of standard SMKI dose taken without food with reduced dose taken with food.[2,19,44,51] To maintain equivalent exposure to 750 mg ceritinib taken fasted, 450 mg and 600 mg doses of ceritinib were administered with a low-fat meal. Administration of 600 mg ceritinib led to a substantially higher exposure compared with 750 mg in the fasted state, but this is however not clinically relevant. Although 450 mg resulted in an equal exposure (4% AUC increase) in comparison to 750 mg taken fasted, less dose reductions occurred (24% *vs* 65%) due to less gastrointestinal toxicity.[19] Conclusively, treatment efficacy in terms of overall response rate, disease control rate, and time to response was shown to be consistent as well.[51] A 2019 study[44] showed that continental breakfast (ie, low-fat meal) consumption with 600 mg pazopanib had similar exposure and toxicity to 800 mg pazopanib administered without food (9% AUC increase). Additionally, in this study, 68% of patients preferred concomitant food intake over fasting. However, the FDA recommendation is intake of both SMKIs without food,[3] whereas EMA's advice is to swallow 450 mg ceritinib with food, or 750 mg pazopanib without food.[2] Considering the better tolerability and economic benefits of a lower dose of ceritinib and pazopanib, both SMKIs (450 mg ceritinib and 600 mg pazopanib) could be administered with a low-fat meal.

Clinical implications

Despite these practical recommendations, not all patients will be able to meet them. For example, if patients cannot eat food or if they are on a special diet, SMKI administration with a meal might be complicated. Fasted intake is possible for SMKIs that are recommended to be taken without food or irrespective of food intake. However, for SMKIs we advise to take with food (to maximise exposure), dose escalation to initial registered doses is an option for ceritinib and pazopanib (table 1). Efficacy data of alectinib and bosutinib, when administered without food, are lacking. Alternative administration routes or even alternative therapies should, therefore, be considered. Because current labels of ibrutinib, lapatinib, and vemurafenib do not oblige food intake, it is still safe to take them without food. Also, for some SMKIs,

therapeutic drug monitoring should be considered to monitor steady-state exposure and optimise dosage.

Ultimately, clinical application of FDIs can be regarded as food-dependent dose individualisation—ie, dosing based on a patient's food consumption. In another 2019 study,[52] by use of therapeutic drug monitoring to determine exposure, pazopanib was administered with a low-fat meal and the dose was escalated or reduced after evaluation of toxicity. With 64% of the initial registered dose of pazopanib, therapeutic target plasma concentrations were reached for multiple cycles.[52] Preferably, pazopanib dose should have been based on its trough concentration. Food-based dose individualisation could then increase SMKI efficacy and lower its drug costs simultaneously. However, high-fat meals should be advised with caution, because fatty acids showed harmful molecular effects, including increased tumour progression and metastasis.[53]

Nowadays, several combination treatments of SMKIs with immunotherapy are under clinical investigation or already used in clinical practice, for instance the combination of axitinib and pembrolizumab in renal cell carinoma.[54] Since immunotherapy is administered parenterally, an FDI with immunotherapy is not expected to occur. However, when food alters the exposure to the co-administered SMKI, total efficacy or toxicity of the combined SMKI-immunotherapy could be affected. Therefore, it is important to be aware of these FDIs when patients have toxic effects from SMKI-immunotherapy combinations, but also when new combinations are investigated.

Most FDI studies use high-fat meals to find the maximal food effect. This effect could, however, be far from the average daily practice, considering that not all patients with cancer are capable of eating high-fat meals. Furthermore, one study found that 21% of patients did not always follow strict fasting recommendations.[55] The effects of this lack of compliance can be considerable. Illustrative for erlotinib, occasional food intake increased its C_{max} by 35% and AUC by 33%, whereas missing a concomitant meal led to a 14% decrease in C_{max} and 15% decrease in AUC.[24] Moreover, other factors, such as therapy compliance, will seriously affect exposure.[55] Hence, FDIs are an important link in the chain to obtain and maintain an adequate systemic drug exposure.

Other pharmacokinetic food effects

The effects of food on the variability and time to reach maximum concentrations of SMKIs are presented in table 2.[2,3,6,10,13–45] Additionally, the absolute bioavailability and biopharmaceutical classification system (BCS) classes are reported in table 3.[2,3,10]

Bioavailability

The absolute bioavailability is the amount of unchanged drug that has been absorbed by the gastrointestinal tract and has entered systemic circulation after hepatic first-pass metabolism. On one hand, when absolute bioavailability is low, a (high-fat) meal could increase absorption and, therefore, could also increase systemic exposure. On the other hand, FDIs could cause a decrease in exposure for the three SMKIs (dabrafenib, imatinib, and ruxolitinib) with a bioavailability of almost 100%. Food does not affect imatinib or ruxolitinib exposure, but decreases the exposure to dabrafenib with 31%.

	Change in C_{max} variability (%)	Change in AUC variability (%)	Change in T_{max} (%; fed T_{max})
(Continued from previous page)			
Nintedanib[2,3]			
High-fat meal	+2%	+63%	+99% (4 h)
Osimertinib[2,3,34,35]			
High-fat meal	+16%	+9%	+33% (8 h)
Pazopanib[2,3,36,44]			
High-fat meal	+23%	+32%	+50% (6 h)
Low-fat meal	–6%	–5%	+50% (6 h)
Low-fat meal (600 mg dose) versus fasted (800 mg dose)	+12%	+6%	+33% (4h)
Ponatinib[2,3,37]			
High-fat meal	–1%	+3%	No effect (6 h)
Low-fat meal	+4%	+5%	–17% (5 h)
Regorafenib[2,3]			
High-fat meal	NA	NA	NA
Low-fat meal	NA	NA	NA
Ruxolitinib[2,3,38]			
High-fat meal	+45%	+9%	+150% (2·5 h)
Sorafenib[2,3]			
High-fat meal	NA	NA	NA
Moderate-fat	NA	NA	NA
Sunitinib[2,3,39]			
High-fat meal	–13%	+3%	+2% (8 h)
Tivozanib[2,4,40]			
High-fat meal	–23%	–1%	+683% (23·5 h)
Trametinib[2,3,41]			
High-fat meal	–12%	+3%	+169% (4 h)
Vandetanib[3,42]			
High-fat meal	No effect	No effect	+33% (8 h)
Vemurafenib[2,3,43]			
High-fat meal	–56%	–49%	+100% (8 h)

C_{max}=maximal plasma concentration. AUC=area under the curve. T_{max}=time to reach C_{max}. NA=not available.

Table 2: **Effect of food on the variability and time to reach maximum concentrations of small-molecule kinase inhibitors**

Biopharmaceutical classification system

The BCS is based on the aqueous solubility of a drug and its intestinal permeability, which are the most important elements affecting drug absorption. BCS classes are divided in four categories: class I drugs have both high solubility and permeability, class II drugs have low solubility and high permeability, class III drugs have high solubility and low permeability, and class IV drugs have both low solubility and permeability.[3] Taking into consideration their solubility limited

	BCS class[2,10]	Bioavailability (%)[2,3,10]
Afatinib	I	NA
Alectinib	IV	37%
Axitinib	II	58%
Binimetinib	I or II*	50%
Bosutinib	IV	34%
Brigatinib	I	NA
Cabozantinib	II	NA
Ceritinib	IV	NA
Cobimetinib	III	46%
Crizotinib	IV	43%
Dabrafenib	II	95%
Dasatinib	II	NA
Encorafenib	II	86%
Erlotinib	II	59%
Gefitinib	II	57–60%
Ibrutinib	II	2·9%
Imatinib	I	98%
Lapatinib	IV	NA
Lenvatinib	II or IV†	85%
Nilotinib	IV	30%
Nintedanib	II	4·7%
Osimertinib	III	70%
Pazopanib	II	21%
Ponatinib	II	NA
Regorafenib	II	NA
Ruxolitinib	I	>95%
Sorafenib	II	NA
Sunitinib	IV	NA
Tivozanib	II or IV†	NA
Trametinib	IV	72%
Vandetanib	II	NA
Vemurafenib	IV	64%

BCS=biopharmaceutical classification system. NA=not available. *Binimetinib shows low solubility (Class II) at physiological pH but higher (Class I) at acidic pH. †Permeability unknown.

Table 3: **Absolute bioavailability and BCS classes of small-molecule kinase inhibitors**

absorption, BCS class II and IV drugs could have more FDIs, because high-fat meals can increase drug solubility. The relative changes in AUC with a high-fat meal are categorised by BCS class in figure 2.[10] Most SMKIs are class II drugs, yet some encounter FDIs, which are both increasing and decreasing exposure. FDI prevalence is balanced in the second largest BCS class (IV), all giving an increased exposure. Albeit only seven SMKIs are BCS classes I or III, only afatinib is negatively affected by food. Hence, high solubility could be associated with lower prevalence of FDIs.

For SMKIs in which absorption is dissolution-limited, a change of formulation to a solid dispersion (ie, small one-phase powder drug particles) could optimise absorption. Therewith, the effect of food and intragastric pH on solubility is reduced.[56]

Time to reach C_{max} (T_{max})

T_{max} is the time when the balance between drug absorption and distribution results in the C_{max}. High-fat meals increased or had no effect on the average T_{max}—eg, for 25 SMKIs a high-fat meal increased T_{max} by 25% or more (table 2). In contrast, other meal types had the potential to decrease T_{max} (eg, for lapatinib and ponatinib). A longer T_{max} could potentially reduce toxicity, because absorption is spread over a longer period. Also, this could prolong gastrointestinal food–drug and drug–drug interaction time. We, therefore, advise specific counselling when patients use interacting drugs or herbs, and administer their SMKI with food.

Variability in exposure

A high-fat meal reduced interpatient variability in AUC by 20% or more for seven SMKIs and increased this variability by 25% or more for two SMKIs (ie, nintedanib and pazopanib). Interpatient variability was similar for pazopanib when administered with a low-fat meal and was regardless of its dose. Furthermore, the majority of SMKIs showed no noteworthy change with food consumption. However, this was measured in different clinical trials in which timing and caloric intake were monitored closely. In real life, the variation in food intake will probably be higher than reported in these clinical trials. Minimal interpatient variability might have favourable clinical consequences, because efficacy and tolerability could be optimal when exposure is within the therapeutic window. As earlier described, food recommendation negligence occurs frequently in daily life and might lead to substantial alterations in exposure.[24,55] Considering the major differences between a study and normal daily life, results of interpatient variability should be interpreted with caution.

Metabolism

After uptake by enterocytes, some SMKIs undergo intestinal metabolism by cytochrome P450 (CYP) isoenzymes. Because most drugs are (largely) metabolised by CYP3A4,[5] most interaction studies are focused on this iso-enzyme. St John's wort strongly induces CYP3A4, therefore, reduces drug bioavailability and exposure. Common foods, such as garlic, red wine, and grapefruit, inhibit CYP3A4,[57] potentially increasing drug exposure.

After reaching the portal vein, SMKIs are metabolised in the liver. Hepatic (phase I) CYP enzymes are responsible for this oxidative metabolism of the majority of SMKIs. As an exception, nintedanib largely undergoes (other phase I) hydrolysis by esterases. Afatinib and binimetinib are mainly metabolised by conjugating phase II enzymes. Lenvatinib and trametinib show predominantly CYP independent phase I and II metabolism (ie, deacetylation, oxidation, and glucuronidation).[2,3]

SMKI metabolism by CYP enzymes mainly results in inactive metabolites. On one hand, CYP induction hence

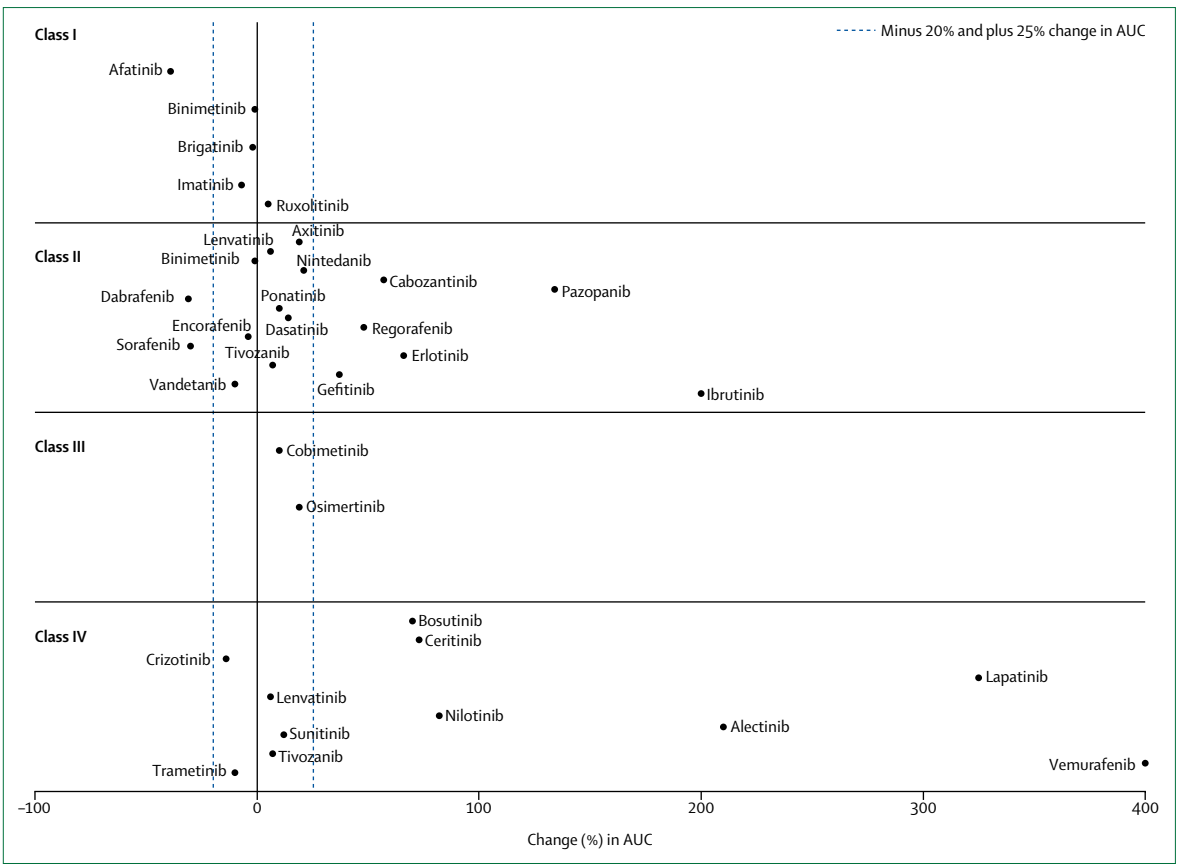

Figure 2: **Relative change in AUC of SMKIs administered with a high-fat meal categorised by BCS class**
Class I drugs have both high solubility and permeability, class II drugs have low solubility and high permeability, class III drugs have high solubility and low permeability, and class IV drugs have both low solubility and permeability. Data derived from table 1 and table 3. The dashed lines represent the minus 20% and plus 25% in AUC wherein no FDI is present. AUC=area under the curve. SMKIs=small-molecule kinase inhibitors. BCS=biopharmaceutical classification system. FDI=food–drug interaction.

leads to decreased exposure with potentially reduced efficacy and toxicity. On the other hand, CYP inhibition increases exposure, which could result in accumulation of potentially life-threatening side-effects. Grapefruit is a widely known comestible inhibitor of hepatic CYP3A4 and St John's is a known inducer of hepatic CYP3A4.

Specific foods

Grapefruit (juice)

Grapefruit is considered to be a strong inhibitor of intestinal and hepatic CYP3A4 and it induces drug efflux by P-glycoprotein transporters.[58] Furthermore, grapefruit's flavonoids (naringin) inhibit the uptake transporter OATP1A2, therefore decreasing drug bioavailability.[59] The high interspecies variability in concentrations of grapefruit's interacting compounds create inconvenient diversity in interaction studies.[60] Results should be carefully interpreted. In general, one single grapefruit or 200 mL or more of grapefruit juice can cause relevant escalation of drug concentrations.[61]

There is, however, a difference between concomitant grapefruit juice intake, which predominantly affects absorption through intestinal CYP inhibition, and chronic (non-concomitant) grapefruit consumption that inhibits hepatic CYP metabolism.[62] The known effects of CYP inducing and inhibiting compounds on SMKI bioavailability are presented in table 4.[2,3,7,63–70] Both the study of sunitinib in humans[70] or the study of sorafenib in rats[68] showed no noteworthy FDIs with chronic grapefruit usage.

Other foods and beverages can have an effect on SMKI bioavailability (table 5).[2,9,27,63,64,71–74] Concomitant grapefruit juice intake was studied for ibrutinib (115% AUC increase),[27] imatinib (2% increase in minimal plasma concentration [C_{min}]),[71] and nilotinib (29% AUC increase).[73] However, since the three study designs are very different, it is difficult to extrapolate their results to other CYP3A4-metabolised SMKIs. FDA and EMA recommendations for all CYP3A4-metabolised SMKIs are to avoid grapefruit. In case of concomitant use, dose reductions are advised for axitinib, brigatinib, cabozantinib, dasatinib, encorafenib, ponatinib, ruxolitinib, and sunitinib, thus minimising potentially dangerous increases of their blood concentration.[2,3] Even in those cases when evidence

	Major CYP	Minor CYP and others	Inhibiting compound	Inducing compound	Recommendations
Afatinib[2,3]	Mainly due to non-enzyme catalysed Michael adduct formation	..	..	..	..
Alectinib[2]	CYP3A4	CYP2C8, CYP3A5	Grapefruit (juice)	St John's wort	When either grapefruit (juice) or St John's wort are co-administered, monitoring is recommended
Axitinib[2,3]	CYP3A4	CYP3A5, CYP1A2, CYP2C19, UGT1A1	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice; when co-administered, decrease dose by approximately 50%); avoid use of St John's wort (when co-administered, a gradual dose increase is recommended)
Binimetinib[2]	UGT1A1	CYP1A2, CYP2C19	..	St John's wort	Avoid use
Bosutinib[2,3]	CYP3A4	Mono-oxygenase enzymes	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice) and of St John's wort
Brigatinib[2,3]	CYP2C8, CYP3A4	CYP3A5	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice; when co-administered, reduce dose by approximately 50%); avoid use of St John's wort
Cabozantinib[2,3]	CYP3A4	CYP2C9	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice; when co-administered, a dose decrease with 33% is recommended); avoid use of St John's wort (when co-administered, a dose decrease with 33% is recommended)
Ceritinib[2,3]	CYP3A4	..	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice) and of St John's wort
Cobimetinib[2,3]	CYP3A4	UGT2B7	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice; when co-administered, monitoring is recommended; interruption when St John's wort is used for less than 8 days should be considered); avoid use of St John's wort
Crizotinib[2,3]	CYP3A4	CYP3A5, CYP2C8, CYP2C19, CYP2D6	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice) and of St John's wort
Dabrafenib[3]	CYP2C8	CYP3A4	..	St John's wort	Avoid use (when co-administered, monitoring is recommended)
Dasatinib[2,3]	CYP3A4	FMO3, UGT	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice; when co-administered, monitoring is recommended; reducing dasatinib dose by 20 mg or 40 mg when total dose is 120 mg or 140 mg daily, respectively, should be considered); avoid use of St John's wort (when co-administered, monitoring is recommended; increasing dasatinib dose shoud be considered)
Encorafenib[2,3]	CYP3A4	CYP2C19, CYP 2D6	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice; when co-administered, reduce dose to 33% of the encorafenib dose); avoid use of St John's wort
Erlotinib[3,63]	CYP3A4	CYP1A2, CYP1A1, CYP1B1, CYP3A5	Grapefruit (juice)	St John's wort; green tea extract (C_{max} 16% and AUC 21%)*	Take caution when grapefruit (juice) is co-administered (dose reduction should be considered when side-effects occur); avoid use of St John's wort; avoid use of green tea extract
Gefitinib[1,2,3,64,65]	CYP3A4, CYP2D6	CYP3A5, CYP2C19	..	St. John's wort; bawu decoction (C_{max} –79% and AUC –61%);* guipi decoction (C_{max} –23% and AUC no effect);* ginseng, mushrooms, and selenium†	Avoid use of St John's wort (dose increase to 500 mg daily should be considered when coadministered); avoid use of bawu decoction; safe to use guipi decoction; avoid use of ginseng, mushrooms, and selenium
Ibrutinib[2,3]	CYP3A4	CYP2D6	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice) and of St John's wort
Imatinib[1,3,7,66,67]	CYP3A4	CYP2C8, CYP3A5, CYP1A2, CYP2D6, CYP2C9, CYP2C19	Grapefruit (juice)	St John's wort (C_{max} –29% to –15% and AUC –32% to –30%); ginseng†	Avoid use of grapefruit (juice); avoid use of St John's wort; avoid use of ginseng (when co-administered, dose should be increased by at least 50% and clinical response should be carefully monitored)
Lapatinib[2,3,63]	CYP3A4	CYP3A5, CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19	Grapefruit (juice)	St John's wort; green tea extract (C_{max} –14% and AUC –22%)*	Avoid use of grapefruit (juice); avoid use of St John's wort (when co-administered, dose should be gradually increased from 1250 to 4500 mg per day and from 1500 to 5500 mg daily); avoid use of green tea extract
Lenvatinib[2,3]	Aldehyde oxidase & gluthatione conjugation	CYP3A4	..	..	..
Nilotinib[2,3]	CYP3A4	CYP2C8, CYP1A1, CYP1A2, CYP1B1	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice) and of St John's wort
Nintedanib[2,3]	Hydrolysis due to esterases	UGT1A1, UGT 1A7, UGT1A8, UGT1A10, CYP3A4	..	St John's wort	Avoid use of St John's wort
Osimertinib[2,3]	CYP3A4	CYP3A5, CYP1A2, CYP2A6, CYP2C9, CYP2E1	..	St John's wort	Avoid use of St John's wort
Pazopanib[2,3]	CYP3A4	CYP1A2, CYP2C8	Grapefruit (juice)	..	Avoid use of grapefruit (juice)

(Table 4 continues on next page)

	Major CYP	Minor CYP and others	Inhibiting compound	Inducing compound	Recommendations
(Continued from previous page)					
Ponatinib[2,3]	CYP3A4	CYP2D6, CYP2C8, CYP3A5	Grapefruit (juice)	St John's wort	When grapefruit (juice) is co-administered, reduce to 30 mg daily; avoid use of St John's wort
Regorafenib[2,3]	CYP3A4	UGT1A9	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice) and of St John's wort
Ruxolitinib[2,3]	CYP3A4	CYP2C9	Grapefruit (juice)	St John's wort	Avoid use of grapefruit (juice; when co-administered, reduce to 10 mg twice daily); concurrent administration should be avoided in patients with <100×10^9 platelets per L; when using St John's wort monitor closely and titrate dose
Sorafenib[3,68,69]	CYP3A4	UGT1A9	Grapefruit (juice) (C_{max} +10% and AUC –16%)*; triptolide (Cmax +44% to +63% and AUC +73% to +83%)*	Long-Dan-Xie-Gan-Tang (C_{max} –4% and AUC –12%);* St John's wort	Avoid use of grapefruit (juice), triptolide, Long-Dan-Xie-Gan-Rang, and St John's wort (when co-administered, consider dose increase)
Sunitinib[2,3,70]	CYP3A4	CYP1A2	Grapefruit (juice) (C_{max} +11% and AUC +11%)	St John's wort	Avoid use of grapefruit (juice; when co-administered, dose decrease should be considered to a minimum of 37·5 mg daily for GIST and mRCC or 25 mg daily for pNET); avoid use of St John's wort (when co-administered, consider dose increase in 12·5 mg increments up to 87·5 mg daily for GIST and mRCC or 62·5 mg daily for pNET)
Tivozanib[2‡]	CYP3A4	UGT1A, CYP1A1	..	St John's wort	Avoid use of St John's wort
Trametinib[2,3]	Deacetylation, oxidation and glucoronidation	CYP3A4	..	..	..
Vandetanib[2]	CYP3A4	FMO1, FMO3	..	St John's wort	Avoid use of St John's wort
Vemurafenib[2]	CYP3A4	UGT	..	St John's wort	Avoid use of St John's wort

C_{max}=maximal plasma concentration. AUC=area under the curve. CYP=cytochrome P450. UGT=UDP-glucuronosyltransferase. FMO=flavine mono-oxygenase. GIST=gastro-intestinal stromal tumour. mRCC=metastatic renal cell carcinomas. pNET=pancreatic neuroendocrine tumours. *In vivo rat study results. †Case report. ‡Only EMA approved.

Table 4: **The effects of CYP inducing and inhibiting compounds on the bioavailability of small-molecule kinase inhibitors**

of FDIs with SMKIs is scarce, we concur with FDA and EMA in the advice to avoid grapefruit completely during SMKI treatment of CYP3A4 substrates, because the composition of grapefruit and subsequent effect on CYP3A4 is variable and unpredictable.

Beverages

Most beverages are known for their low pH and high-sugar content.[75] Because of its phosphoric acid ingredient, cola was found to be acidic enough to overcome the drug–drug interaction with erlotinib and a proton-pump inhibitor.[9] Most soda, fruit, and energy drinks have a mean pH less than 4, making them suitable for researching similar purposes.[75] Likewise, hypothetically exploring erlotinib's lipophilicity, a potential FDI with fatty milk was studied. (ESMO 2019, #1540P)[76] Since no FDI was found, erlotinib administration with milk is safe. Furthermore, green tea extract caused major FDIs with erlotinib, lapatinib, and sunitinib in rats, decreasing their AUCs by 51–74%.[63,74] We thus recommend avoiding green tea extract during SMKI therapy until proven safe in humans. Nonetheless, some patients with cancer are not capable of taking their SMKI with water. In that specific situation, albeit only proven for nilotinib, administration with a teaspoon of non-fat plain yoghurt or applesauce is considered safe,[2,72] and we would extrapolate those outcomes to all SMKIs.

Herb–drug interactions

St John's wort

St John's wort (*Hypericum perforatum*) is frequently used as an antidepressive compound. Its active substance, hyperforin, induces hepatic CYP3A4 and inhibits P-glycoprotein mediated drug efflux.[12,77] Clinical and pharmacokinetic effects have been proven to be positively associated with hyperforin concentrations in different studies.[77] St John's wort's HDI was investigated in two clinical trials that showed a 30–32% decrease in drug exposure following consumption of St John's wort (table 4).[7,67] Because concentrations of active substances fluctuate by 5–8 times between brands or abstracts,[77] standardisation of study methods to investigate the HDI for all SMKIs is very difficult. Therefore, we recommend avoiding consumption of St John's wort during SMKI treatment, which is in accordance with FDA and EMA recommendations.[2,3]

Oriental herbs

Herbal products are used by 13–63% of patients with cancer. Up to 72% of these patients do not inform their oncologist about their supplemental herb intake, therefore interaction potential with conventional anticancer treatment may be substantial.[8] Much is unknown about HDIs with SMKIs in clinical practice. Numerous oriental herbs can inhibit multiple CYP-enzymes,[8] though no

	Study intervention	Change in C_{max}	Change in C_{max} variability (%)	Change in AUC	Change in AUC relative variability (%)	Change in T_{max} % (fed T_{max})	Importance*	Recommendations
Erlotinib								
Green tea (extract)[63]†	Single-dose erlotinib immediately after green tea extract	–68%	214%	–70%	–12%	No effect (1 h)	Major	Avoid use of green tea (extract)
Coca-Cola[9]	Multiple doses of erlotinib with Coca-Cola	No effect	–6%	+9%	–9%	+16% (NA)	Minor	Safe to use
Coca-Cola[9]	Multiple doses of erlotinib with esomeprazol and Coca-Cola	+42%	–26%	+39%	–25%	No effect (NA)	Major	Consider taking with Coca-Cola when using PPI or take PPI >3 h after erlotinib
Gefitinib								
Bawu decoction[64]†	Single-dose gefitinib 5 min and 1 h after herb	–88% to –67%	+35% to 92%	–75% to –60%	–57% to –17%	+271% to 393% (5·2 to 7·4 h)	Major	Avoid use
Guipi decoction[64]†	Single-dose gefitinib 5 min and 1 h after herb	–36% to –22%	+28% to 78%	–21% to –19%	–6% to +17%	–7% to +60% (1·3 to 2·4 h)	Moderate	Avoid concomitant administration
Ibrutinib								
Grapefruit juice[27]	Single-dose ibrutinib the evening before and concomitant grapefruit juice	+260%	+52%	+115%	+57%	–15% (1·5 h)	Major	Avoid use of grapefruit (juice)
Imatinib								
Grapefruit juice[71]	Multiple doses of imatinib concomitant grapefruit juice	–2%	NA	NA; C_{min} +2%	NA	NA	Minor	Avoid grapefruit (juice), since its composition is variable and unpredictable
Lapatinib								
Green tea (extract)[63]†	Single-dose lapatinib immediately after green tea extract	–70%	+235%	–74%	–47%	No effect (1 h)	Major	Avoid use of green tea (extract)
Nilotinib								
Grapefruit juice[73]	Single-dose nilotinib with grapefruit juice	+60%	–26%	+29%	–14%	No effect (4 h)	Moderate	Avoid use of grapefruit (juice)
Non-fat plain yoghurt[2,72]	Single-dose nilotinib with non-fat plain yoghurt	+31%	–6%	+8%	+2%	No effect (4 h)	Minor	Safe to use
Applesauce[2,72]	Single-dose nilotinib with applesauce	–5%	+3%	–3%	–8%	–25% (3 h)	Minor	Safe to use
Sunitinib								
Green tea (extract)[74]†	Single-dose sunitinib concomitant with green tea polyphenol epigallocatechin-3-gallate	–48%	–46%	–51%	–24%	+37% (4·9 h)	Major	Avoid use of green tea (extract)

Only small-molecule kinase inhibitors with known interactions are shown in this table. C_{max}=maximal plasma concentration. C_{min}=minimal plasma concentration. AUC=area under the curve. NA=not available. PPI=proton-pump inhibitor. *Importance of the food-drug interaction is considered minor (not clinically relevant) when AUC is <20% decreased or <25% increased, moderate when AUC is ≥20% and <50% decreased or ≥25% and <67% increased and major when AUC is ≥67% increased or ≥50% decreased. †In vivo rat study results.

Table 5: **The effects of other foods and beverages on the bioavailability of small-molecule kinase inhibitors**

standardised HDI studies in humans with SMKIs were found (tables 4, 5). Two case reports describe reversible severe toxicity and therapy failure, probably due to ginseng (potential CYP-inducer) and other alternative preparations.[65,66] The decoctions bawu and guipi are traditional oriental medicines. Bawu is a mixture of eight herbs and guipi is a mixture of 12 herbs, both include ginseng. These traditional medicines are considered to be purifying and are used to treat various diseases. Bawu decreased gefitinib's AUC in rats by 61–75%, without regard to administration time.[64] Guipi was found not to have an HDI when co-administration with gefitinib was avoided, because it caused a 21% decrease in gefitinib exposure otherwise.[64] Triptolide (derived from *Tripterygium wilfordii*) escalated sorafenib's AUC with 83% in rats, possibly through CYP3A4 inhibition.[69]

EMA and FDA recommendations for SMKIs do not specifically mention safe or dangerous herbal preparations, but patients are instructed to communicate herb use to their health-care provider.[2,3] Because conclusive data are missing, clinicians are faced with questions that are practically unanswerable. Current advice is to avoid products with possible interacting compounds, to minimise the risk of HDIs. To provide clinicians and patients clear recommendations concerning the dangers or safety of herbal preparations, more research to HDIs and SMKIs is warranted.

Food–drug interaction studies

Registered therapeutic doses of SMKI are generally based on the maximum tolerated dose that is found in phase I trials. Once a decision is made for SMKI administration in fed or fasted state, all consecutive registration studies maintain this food recommendation. To change these recommendations, for instance to reduce drug costs by allowing food consumption with a reduced dose, solid evidence that FDIs affect drug tolerability or anticancer activity must be shown. Since toxicity develops generally after a loading phase of several weeks, FDI studies should ideally include multiple drug doses over a long period (ie, multiple weeks). Phase I studies can be used for this purpose. In studies in which an FDI is present, repeating the drug's registration studies from phase I to phase III can guarantee safety and efficacy. Single-dose FDI studies, which miss a reliable safety and efficacy assessment of the loading phase, are thus limited for extrapolation of established FDIs to clinical recommendations. Their strength solely lies in the exclusion of an FDI, when no clinically significant change in exposure is found. The FDA, however, recommends only a single-dose study design to research FDIs.[3]

Currently, popularity of calorie-restricted dietary interventions, such as cyclic fasting or fasting-mimicking diets, is increasing. Their safety and effectivity are being investigated in various clinical trials (NCT03340935, NL5624, and NCT03595540), because much is unknown about their efficacy and potential pharmacokinetic effect on anticancer drugs.

Animal models are not suited as replacement for human in-vivo studies, because interspecies differences can bias FDIs. For example, no FDI for gefitinib (in dogs) and pazopanib (in monkeys) was found,[2] whereas in humans there is a food effect (table 1). The relevance of in-vitro data for HDIs is limited, although some prediction models that mimic HDIs (eg, midazolam as model substrate for CYP3A4) show promising results and could be feasible.[7,8] In-vitro research could be used as an indicator to identify herbs that should be studied in vivo, as requested by EMA.[2] We recommend studying in-vivo FDIs and HDIs at steady state, with a multiple-dose instead of a single-dose study, with enough patients or healthy volunteers to examine exposure with subsequent efficacy and tolerability. Results of such studies would be conclusive for providing useful advice for clinical practice.

Search strategy and selection criteria

A literature search for European Medicines Agency-approved small-molecule kinase inhibitors (SMKIs) used in haemato-oncology, with the exception of mTOR- and CDK4/6-inhibitors, was done in Embase and Pubmed from database inception until Oct 1, 2019, using the MESH terms: "(food-drug interactions) OR (herb-drug combination) OR ((complementary therapies OR combination OR interaction OR supplement) AND (diet OR food OR herb OR drink)) AND (drug name)". In Embase, we applicated "clinical studies", "humans", and "only in English" as quick search limits. Prior to full-text screening, abstracts and titles were screened. Also, articles concerning pharmacokinetic effects of possible in-vivo FDIs or HDIs were included. FDA and EMA assessment reports (including updates) and "Summary of Product Characteristics" were additionally examined for FDIs and HDIs for each SMKI. Practical recommendations were formulated based on available evidence and the FDA's definition of an FDI.

Conclusions

FDIs and HDIs can alter the systemic bioavailability and pharmacokinetics of many clinically approved SMKIs. The major mechanisms underlying FDIs and HDIs concern gastrointestinal drug absorption and metabolism through cytochrome P450 isoenzymes. FDIs and HDIs might lead to therapy failure or (acute) severe toxicity, therefore knowledge of these interactions is essential.

Contributors

GDMV, KGAMH, FGAJ, RWFvL, and RHJM developed the concept and design for this Review. GDMV, KGAMH, and FGAJ collected and assembled the data. GDMV led the writing. KGAMH, FGAJ, SWLK, RWFvL, and RHJM were responsible for critical revisions. All authors contributed to data analysis and interpretation, creation of figures and tables, and preparation of the report for publication and they approved the final version of the manuscript.

Declaration of interests

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