Clinical pharmacology of the tyrosine kinase inhibitors imatinib and sunitinib

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Clinically irrelevant effect of Grapefruit Juice on the steady-state sunitinib exposure

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Abstract

Purpose: To determine the effect of grapefruit juice, a potent intestinal cytochrome P450 3A4 (CYP3A4) inhibitor, on steady-state sunitinib pharmacokinetics (PK).

Methods: Sunitinib PK were evaluated in cancer patients receiving sunitinib monotherapy in a "four weeks on - 2 weeks off" dose regimen. Serial blood samples for PK analysis of sunitinib were collected on two separate days. On both PK days patients received a single oral dose of 7.5 mg midazolam as a phenotypic probe for intestinal CYP3A4 activity. The first PK day was at steady-state sunitinib PK (between days 14-20), the second PK day was on day 28. On day 25, 26 and 27, 200 mL grapefruit juice was consumed three times a day. The effect of grapefruit juice on sunitinib exposure was assessed by comparing sunitinib pharmacokinetics on both PK days.

Results: In 8 patients the effect of grapefruit juice on sunitinib exposure was evaluated. Concomitant use of grapefruit juice and sunitinib resulted in an 11% increase of the relative bioavailability of sunitinib ($P < .05$). The effect of grapefruit juice on CYP3A4 activity was confirmed by an approximate increase of 50% in mean midazolam exposure ($AUC_{0\text{-}24hr}$) from 122.1 ng*hr/mL to 182.0 ng*hr/mL ($P = .034$).

Conclusion: Grapefruit juice consumption results in a marginal increase in sunitinib exposure which was not considered clinically relevant. Therefore, the warning in the sunitinib drug label for concomitant use of grapefruit juice should be reconsidered.

Introduction

Sunitinib malate (Sutent®; SU11248) is a multitarget tyrosine kinase inhibitor registered for the first line treatment of metastatic renal cell carcinoma (mRCC) and imatinib-resistant metastatic gastrointestinal stromal tumors (GIST).[1-3] The approved dosing regimen for sunitinib is a "four weeks on – two weeks off" schedule.[4] Sunitinib is absorbed from the gastrointestinal tract to an unknown extent. The intake of food does not affect the pharmacokinetics of sunitinib.[5] Sunitinib is *in vitro* extensively protein bound, has a long half-life of ~50 hours and a large apparent volume of distribution of ~2000 liters.[3, 6] Cytochrome P450 3A4 (CYP3A4) metabolizes sunitinib into an active metabolite, SU12662, which is further metabolized by CYP3A4 into inactive moieties.[3, 7, 8] Sunitinib has not been described to be a substrate of any other metabolizing enzymes besides CYP3A4. It was identified *in vitro* as a moderate substrate of the ATP-binding cassette (ABC) drug transporters ABCG2 and ABCB1 and showed no affinity for organic anion transporting polypeptides (OATPs). However, the clinical relevance of these transporters on the disposition *in vivo* needs to be addressed.[9, 10]

Co-administration of ketoconazol, a potent CYP3A4 inhibitor, resulted in a 51% increase of the combined area under the concentration time curve (AUC) of sunitinib and SU12662 after a single dose of sunitinib in healthy volunteers.[3] This observation was extrapolated to warnings for the potential effect of strong CYP3A4 inhibitors including grapefruit juice in the drug label of sunitinib[8].

Grapefruit juice contains a rich mixture of several hundred ingredients which may be responsible for the grapefruit juice – drug interaction effect.[11-14] By administering the purified forms of the different compounds to human volunteers, the furanocoumarins (mostly bergamottin (BG) and 6',7'-dihydroxybergamottin (DHB)) were confirmed to result in a significant CYP3A4 inhibiting effect.[15-17] Grapefruit juice is an inhibitor of intestinal CYP3A4, with little effect on hepatic CYP3A4 activity.[18] Grapefruit juice also appears to be an inhibitor of ABCB1 and possibly of OATP located in the intestines.[17-20]

Recently, multiple oral anticancer therapies, mainly tyrosine kinase inhibitors, were introduced and since most of them are substrates of CYP3A4, their drug label contains a warning against the consumption of grapefruit juice. Sofar, only one study has determined the effect of grapefruit juice on an oral anticancer drug (etoposide).[21] In this study an opposite effect of grapefruit juice was observed. Since more patients will be treated with oral anticancer therapy in the future, it is relevant to better understand and determine the clinical relevance of an effect of grapefruit juice on oral anticancer therapy exposure. Therefore, in this study the effect of grapefruit juice on the steady-state sunitinib exposure in cancer patients was determined.

Methods

Patients

Patients eligible for study entry were treated with sunitinib at a dose level of 25 – 50 mg once daily in a "four weeks on – two weeks off" regimen. All patients were ≥ 18 years old, had a WHO performance status ≤ 2 and a life expectancy of at least 12 weeks. Cytotoxic chemotherapy or radiation therapy within four weeks before entering the study protocol was not allowed. Concurrent use of substances known or likely to interfere with the pharmacokinetics of sunitinib and with CYP3A4 activity, such as ketoconazol, fluconazol, rifampicin and St. John's wort, were not allowed within 14 days before study entry and during the study. All patients had adequate bone marrow, renal and hepatic functions as defined by hemoglobin ≥ 6.0 mmol/L, WBC ≥ 3.0 × 10^9/L, platelets ≥ 100 × 10^9/L, creatinine clearance ≥ 60 mL/min and bilirubin ≤ 1.75 × the upper limit of institutional normal range. Prior to commencing the study, a sample size of 8 patients was determined as sufficient for a paired, two sided analysis to detect a difference of 25% in sunitinib exposure with a power (1-β) of 0.8 (80%), and a two-sided significance level (α) of 0.05 (5%). The study was approved by the institutional ethics committee (Leiden University Medical Center, The Netherlands), and all patients gave written informed consent before entering the study.

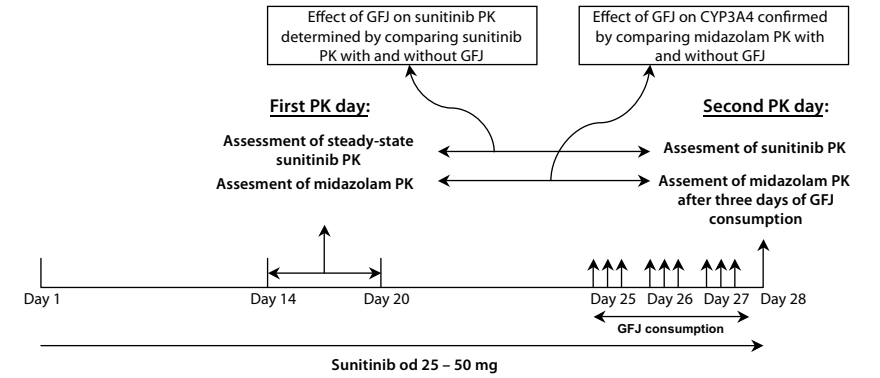
Study design

The study was designed to evaluate the effect of grapefruit juice on steady-state sunitinib pharmacokinetics. All patients were treated with commercially available sunitinib malate hard capsule (Pfizer, Kent, United Kingdom) at an oral dose of 25 – 50 mg once daily in a "four weeks on followed by two weeks off" dose regimen. The study was performed during one sunitinib treatment cycle of six weeks. Patients were admitted to the hospital on two separate PK days. The first PK day was at steady-state sunitinib PK (between day 14 - 20) and the second PK day was on day 28. On days 25, 26, and 27, the patients took 200 ml grapefruit juice of a preselected lot of commercially available grapefruit juice three times daily. On these three days, sunitinib was simultaneously used with the morning consumption of the grapefruit juice. On both PK days patients were given one midazolam 7.5 mg tablet (Roche, Woerden, The Netherlands) as a phenotypic probe to confirm the inhibitory effect of grapefruit juice on intestinal CYP3A4 activity (Fig. 1).

Selection of a grapefruit juice batch

Different batches of grapefruit juice show a considerable variability in BG (~35 fold) and DHB (~200 fold) concentration.[22] Therefore selecting a batch with a sufficient amount of BG and DHB to induce a clinically relevant effect on CYP3A4 substrates was necessary before the interaction study was conducted.[15]

Figure 1 Study design



Abbreviations: GFJ = grapefruit juice; PK = pharmacokinetics; od = once daily

Concentrations of BG and DHB were quantified in various batches of grapefruit juice from different brands using a validated high pressure liquid chromatography – ultraviolet detection (HPLC-UV) method. This assay was based on a previously published method with minor modifications.[22] Briefly, the juice was homogenized by shaking. Grapefruit juice (0.5mL) was mixed with 10 μL internal standard fenprocoumon (100 μg/mL, in methanol) and 2 mL ethyl acetate. Calibration standards contained 0.2 – 4 μg/mL BG and 0.1 – 2 μg/mL DHB were prepared at the start of each analytical run. The standard stock solution contained BG and DHB (100 and 50 μg/mL in DMSO:methanol(1:3)). The residue from the organic phase was reconstituted with 100 μL of DMSO/acetonitril solution (1:3 v/v) and applied to a HPLC separation system (Unexas 2104, Knauer, Berlin, Germany). The compounds of interest were separated on a Hypersil ODS RP analytical column (4.6 x 100 mm, i.d 3 μm) using the following gradient [time scale (minutes - minutes)/ percentage of solvent A (water 2500/ phosphoric acid 1.25)/ percentage of solvent B (acetonitril)]: 0-7/70/30, 7-17 70/30 → 0/100, 17-18/0/100, 18-19 0/100 → 70/30, 19-22/70/30. DHB, fenprocoumon and BG eluted at 10.9, 12.8 and 16.5 minutes, respectively. Linearity was confirmed over the range of 0.2 – 24 μg/mL for BG and 0.1 – 12 μg/mL for DHB. The within day and between day precision and accuracy were < 15%.

Pharmacokinetic sampling

Blood samples were collected on the first and second PK day of the study for assessing sunitinib and midazolam plasma concentrations. Blood was collected in heparin-containing

tubes at the following time points: pre-dose, 10, 20, 40 minutes; 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours after simultaneous intake of sunitinib and midazolam. Blood samples were centrifuged at 3,000 rpm for 10 minutes and plasma was stored at –80˚C until the day of analysis.

Bioanalysis of sunitinib and midazolam

Sunitinib was measured using a validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) assay, which has been described earlier.[23] The calibration curve of sunitinib is linear over the range of 0.2 – 500 ng/mL. The within day and between day precision and accuracy were < 8%. The LLQ of the sunitinib assay was 0.2 ng/mL.

Midazolam was measured using a validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) assay. Briefly, 200 μl plasma was extracted by adding 500 μl of acetonitril containing midazolam D4 (4μg/L) as the internal standard, followed by vortex mixing and centrifugation at 13,000 rpm for 5 minutes at ambient temperature. The supernatant was collected and 10 μL was separated on an Atlantis T3 C18 analytical column (2.1 x 50 mm, i.d 3 μm) and eluted with the following gradient [flow rate (ml/min)/ time (minutes)/ percentage of solvent A (formic acid 0.1% in water)/ percentage of solvent B (formic acid 0.1% in acetonitril)]: 0.3/0.5/85/15/, 0.3/1/10/90, 0.3/4.3/10/90, 0.5/0.01/10/90, 0.5/0.39/85/15, 0.5/3.3/85/15, 0.3/0.05/85/15, 0.3/0.05/85/15. The effluent was monitored with a Micromass Quattro LC triple-quadrupole mass-spectrometric detector (Waters, Milford, MA, USA) using the electrospray positive ionization mode. The calibration curve of midazolam was linear over the range of 1 – 100 ng/mL. The within day and between day precision and accuracy were < 5%. The LLQ of the midazolam assay was 0.3 ng/mL.

Pharmacokinetic analysis of midazolam

Midazolam plasma concentrations were analyzed by non-compartimental methods using WinNonlin (version 5.2.1) (Pharsight Corporation, Mountain View, CA, USA). The midazolam area under the concentration time curve ($AUC_{0\text{-}24hr}$) was calculated and was compared between the first and second PK days. Statistical analysis included the two-tailed paired Student's *t*-test, and *P* values < 0.05 were considered statistically significant. The statistical calculations were performed using SPSS 16.0 (SPSS Inc. headquarters, Chicago, Illinois, USA)

Pharmacokinetic analysis of sunitinib

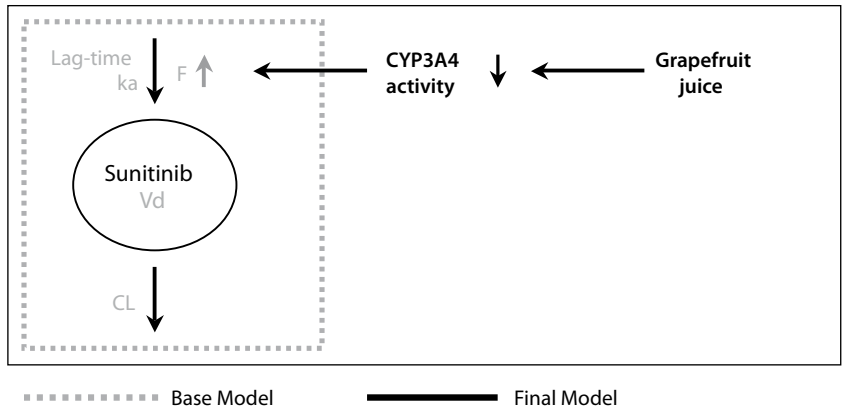
Sunitinib plasma concentrations were evaluated by a population pharmacokinetic method using NONMEM (version VI, level 1.0) (Globomax, Hanover, MD, USA). The First-Order Conditional Estimation (FOCE) method of NONMEM with interaction (INTER) between the interindividual and residual random effects was used.[24] Discrimination between hierarchical models was based on comparison of the objective function values (OFV) of NONMEM using the likelihood ratio test. A decrease in ΔOFV of 3.84 (=*P* < .05) was considered statistical significant.

A base model was developed to describe sunitinib pharmacokinetics, using sunitinib concentrations obtained on the first and second PK day. Next, a final model was developed by the introduction of a grapefruit juice effect on the relative bioavailability of sunitinib, resulting in an effect on the apparent clearance and apparent volume of distribution and thereby exposure to sunitinib, since it was hypothesized that grapefruit juice exerts its effect only by irreversible inhibition of intestinal CYP3A4 and possibly by inhibition of ABCB1 (Fig. 2). The recovery half life of CYP3A4 activity after grapefruit juice consumption was set to 23 hours.[25]

The model was evaluated by goodness of fit plots, case deletion diagnostics and a numerical predictive check. Moreover, a log-likelihood profile was generated for the effect size of grapefruit juice to determine the confidence interval.

The effect of grapefruit juice on sunitinib bioavailability was evaluated for various scenarios: 1) simultaneous intake of sunitinib and grapefruit juice, 2) sunitinib intake 7 hours, 3) 24 hours, 4) 72 hours and 5) one week after the last grapefruit juice consumption.

Figure 2 Sunitinib pharmacokinetic model



Results

Patients

Eight patients were enrolled into the study. All were evaluable for PK analysis. Patient characteristics are summarized in Table 1. No severe or unexpected side effects were observed during the three days of grapefruit juice co-administration or by midazolam co-administration on both PK days.

Table I Patient characteristics

Characteristic	Value
Number of patients	8
Sex (female / male)	1/7
Age, years*	54 (41 - 78)
Baseline serum renal and liver function parameters	
Creatinine, μM*	77 (56 - 122)
Total bilirubin, μM*	9 (6 - 15)
ALT, units/L*	39 (18 - 68)
Baseline bone marrow function parameters	
Hb, mM*	8.7 (7 - 9.4)
WBC, x 10^9/L*	5.5 (3.5 - 38.2)
Thrombocytes, x 10^9/L*	196 (149 - 318)

* Median values (range)

Selection of grapefruit juice

The concentration of BG and DHB was measured in 6 different lots of grapefruit juice. BG and DHB concentrations among the lots tested varied with ~4.5 fold and ~20 fold, respectively. The concentration of BG and DHB in the selected lot of grapefruit juice was 33.1 μmol/L and 2.7 μmol/L, respectively, corresponding with 2.2 mg/200mL BG and 0.2 mg/200mL DHB. Due to the expiration date a second lot of the same brand was selected for the last two patients of the study. The concentrations in the second lot selected were 23.5 μmol/L BG and 5.7 μmol/L DHB, corresponding with 1.6 mg/200mL BG and 0.4 mg/200mL DHB. The concentration of BG in both lots was sufficient to induce a significant drug interaction.[15]

Pharmacokinetic analysis of midazolam

Midazolam exposure ($AUC_{0\text{-}24hr}$) increased after prior intake of grapefruit juice. The midazolam exposure expressed as $AUC_{0\text{-}24hr}$ (± standard error of the mean (SEM)) with and without grapefruit juice were 122.1 (± 32.9) ng*hr/mL and 182.0 (± 52.2) ng*hr/mL, respectively (*P*-value = .034). Thereby, midazolam exposure increased with ~50% in the presence of grapefruit juice. These results confirm the inhibitory effect of grapefruit juice on intestinal CYP3A4 activity.

Pharmacokinetic analysis of sunitinib

A one-compartment model with linear elimination and first-order absorption adequately described the time profile of sunitinib concentrations. The data did not contain sufficient information to support a two-compartment model[6]. Inclusion of an absorption lag time significantly improved the base model of sunitinib. Between-subject variabilities of the absorption rate and clearance were large (60-70%). The base model of sunitinib is graphically presented in Figure 2 (left side).

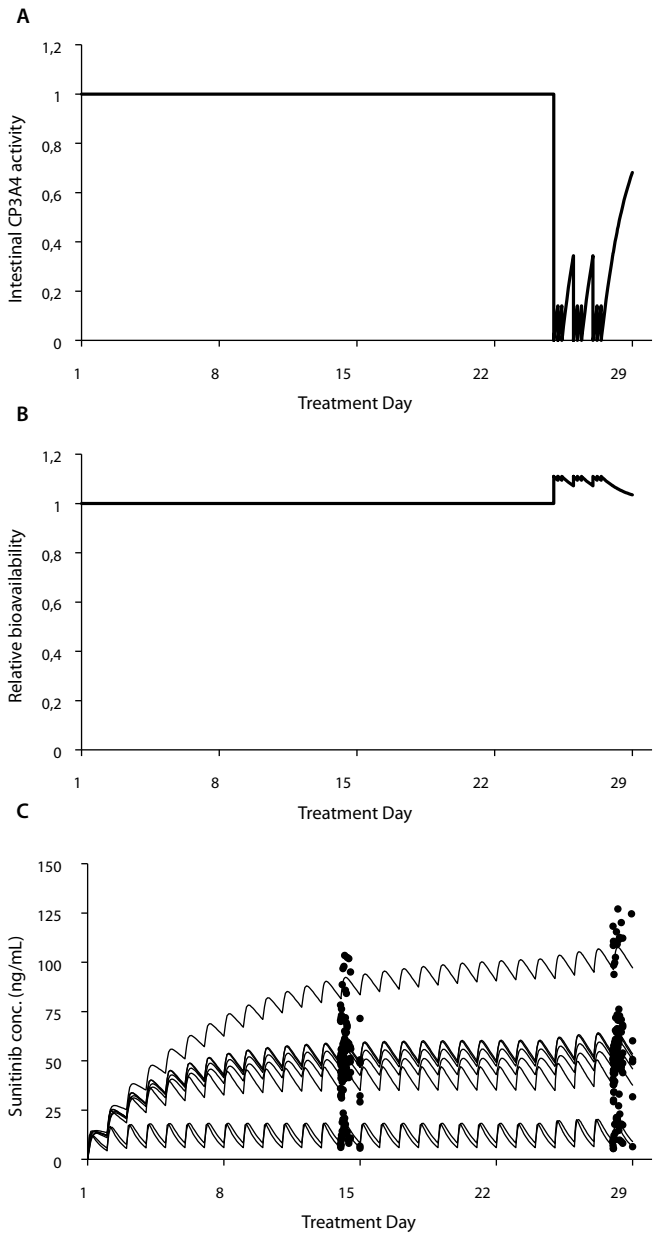
In the final model, CYP3A4 activity was depleted by each grapefruit juice consumption (9 in total) and the activity was restored with a half life of 23 hours (Fig. 3A).[25] Inhibition of CYP3A4 activity resulted in an increase in the relative bioavailability of sunitinib (Fig. 3B). The individual predicted and measured sunitinib concentrations are depicted for all patients (Fig. 3C). Introduction of the grapefruit juice effect on the relative bioavailability of sunitinib significantly improved the model (ΔOFV = -10.01, $P < .05$) and resulted in the final model (Fig. 2).

The estimated pharmacokinetic parameters in the final model are listed in Table 2. The derived parameters are calculated with the estimated pharmacokinetic parameters and represent the data when grapefruit juice and sunitinib are used simultaneously. Goodness-of-fit plots demonstrated that the final model adequately described the time profile of sunitinib concentrations. Case deletion diagnostics demonstrated that the estimated grapefruit juice effect was not highly dependent on the data from a single patient (range in relative F = 1.05 – 1.14). Moreover, suitability of the final model was confirmed by the results from a numerical predictive check.[26] Out of 268 observed sunitinib concentrations, 21.6% were below the P25-P75 (interquartile) prediction interval, 57.1% were within the interval and 21.3% was above the P25-P75 prediction interval.

Based on the final model it is determined that simultaneous intake of sunitinib and grapefruit juice results in a decrease of intestinal CYP3A4 activity and a consequent increase of sunitinib exposure of 11% (as a result of the increased relative bioavailability 1.11, 95%CI: 1.042-1.082).

Since the intestinal CYP3A4 activity is restored with a half-life of 23 hours, the relative bioavailability of sunitinib is also restored with a half-life of 23 hours. The different time interval evaluations resulted in the following estimates: when grapefruit juice is consumed 7 hours before the sunitinib dose, the exposure is still increased by ~8.9%, after 24 hours the effect is diminished to ~5.3% and after 72 hours to ~1.3%. If sunitinib therapy starts one week after the last grapefruit juice consumption the effect of grapefruit juice on the exposure to sunitinib is negligible (~0.07%).

Figure 3 Effect of grapefruit juice on sunitinib pharmacokinetics



A: Depletion of CYP3A4 activity by grapefruit juice consumption. **B**: Increase in relative bioavailability of sunitinib by grapefruit juice consumption. **C**: Individual predicted (lines) and measured (solid marks) sunitinib concentrations

Table 2 Estimated and derived sunitinib pharmacokinetic parameters in the final model

Estimated Parameters	Estimate	Standard Error of Estimate (RSE%)	Interindividual variability (IIV)(CV%)	Standard Error of IIV (RSE%)
Cl/F (L/hr)	50.5	28.5	67.9	42.7
Vd/F (L)	3210	7.8	nd	nd
ka (hr^{-1})	0.468	29.1	63.9	42.9
Relative F	1.11	70	nd	nd
Absorption lag time (hr)	0.487	7.3	nd	nd
Proportional residual error (%)	16.3	22.9	nd	nd

Derived Parameters*	Sunitinib without grapefruit juice	Sunitinib with grapefruit juice when simultaneously taken
$AUC_{0\text{-}24hr}$ (ng*hr/mL)	1122 (277 – 2399)	1245 (308 – 2663)
C_{max} (ng/mL)	13.0 (10.0 – 14.6)	14.4 (11.1 – 16.2)
$t_{1/2}$ (hr)	53 (12 – 107)	
T_{max} (hr)	8.2 (2.8 – 12.4)	

Abbreviations: RSE = relative standard error; Cl/F = apparent clearance; Vd/F = apparent volume of distribution; ka = absorption rate constant; F = bioavailability; nd = not determined; $AUC_{0\text{-}24hr}$ = area under the plasma concentration-time curve over the dose interval 0-24hr at steady-state pharmacokinetics; $t_{1/2}$ = elimination half-life; T_{max} = time to reach peak plasma concentration. Between-subject variability was assessed using exponential models.

* Derived parameters are calculated from estimated parameters and are demonstrated as mean values (range).

Discussion

This study shows that inhibition of the intestinal CYP3A4 activity by grapefruit juice results in a significant but not clinically relevant increase in the sunitinib exposure. The drug label of sunitinib includes the advice to avoid the consumption of grapefruit juice during sunitinib treatment. This warning is based upon an extrapolation of the effect of ketoconazol on sunitinib exposure after single dose administration. Our study is the first to directly investigate the effect of grapefruit juice on sunitinib exposure in cancer patients under steady-state conditions and shows that there is no scientific basis for the warning in the sunitinib's drug label.

Moreover, this is the second study investigating an interaction of grapefruit juice with oral anticancer therapy and both studies show an irrelevant effect of grapefruit juice which contrasts the warning in the drug label[21]. All eight registered tyrosine kinase inhibitors are substrates of CYP3A4 and therefore include the warning for consuming grapefruit juice in their drug label. This is the first study that shows a clinically irrelevant effect of grapefruit juice on one of the tyrosine kinase inhibitors, sunitinib, which could also be relevant for the other TKIs.

Grapefruit juice is a potent inhibitor of intestinal CYP3A4 with little effect on the activity of hepatic CYP3A4. The affinity for only intestinal CYP3A4 was concluded from the significant effect grapefruit juice has on the exposure to CYP3A4 substrates (e.g. simvastatin, felodipine, triazolam) after oral administration, while the effect was only limited after intravenous administration of these drugs.[15, 27-29] Grapefruit juice is also an inhibitor of the drug transporters ABCB1, OATP1A2 and OATP2B1, which could contribute to the effect of grapefruit juice on the exposure of co-administered drugs.[13, 30-35]

Midazolam is extensively metabolized by CYP3A4 with less affinity for CYP3A5, and is not transported by ABCB1, ABCG2 and OATPs[36-39]. In previous studies, grapefruit juice showed a pronounced effect on the exposure of orally administered midazolam[25, 29, 40]. In this study, midazolam was co-administrated on both PK days as a phenotypic probe to confirm the decreased activity of intestinal CYP3A4 by the selected batch of grapefruit juice.

The patients in our study consumed grapefruit juice three times a day for three days (25, 26, and 27) at steady-state. On the last sunitinib treatment day (day 28) in the six week treatment cycle, the sunitinib PK was determined and compared to the data obtained without the exposure to grapefruit juice. The effect of grapefruit juice was estimated on the relative bioavailability of sunitinib, since grapefruit juice is a potent intestinal CYP3A4 inhibitor and therefore, only an effect on the sunitinib uptake is expected rather than on sunitinib clearance, volume of distribution, absorption rate constant and lag time. Indeed the concomitant use of grapefruit juice results in a significant increase of 11% in sunitinib exposure. However, since the reported interpatient variability in sunitinib clearance is large ~ 40% the effect of grapefruit juice on sunitinib exposure is negligible and should not be regarded as clinically relevant.[6] Moreover, the marginal 11% increase in sunitinib exposure is unlikely to result in a different toxicity profile or treatment efficacy, although data on the drug exposure – treatment outcome and toxicity response relation are not available yet.

Grapefruit juice irreversibly inhibits CYP3A4 and it therefore takes time to restore CYP3A4 functionality since new enzymes needs to be formed. The recovery half-life of CYP3A4 activity after consuming grapefruit juice was set to 23 hours according to the recovery study of Greenblatt et al.[14] The recovery half-life was confirmed by several interaction studies between midazolam and grapefruit juice over different time intervals[29, 40, 41].

The half-life of sunitinib is long (~50 hours). Steady-state sunitinib PK is therefore achieved within ~ 8 days. After starting grapefruit juice consumption is takes ~ 8 days to achieve new steady-state sunitinib PK. At the second PK day, after three days co-administration of grapefruit juice, a new steady-state was not reached yet. Since a large effect, and thereby potential toxicity, was hypothesized it was considered unethical to continue the co-administration until steady-state sunitinib PK was reached. Due to this study design the effect of grapefruit juice on sunitinib pharmacokinetics could only be estimated by a compartmental approach. The estimated apparent clearance and volume of distribution are similar to the described parameters of an earlier published compartmental approach.[6] Conversely, a non-compartimental approach was used for determining midazolam exposure after a single dose of 7.5mg. Since, only an exposure difference in midazolam was required to determine the effect of grapefruit juice, which could adequately be determined by a non-compartimental approach due to extensive sampling from start until undetectable levels of midazolam were measured.

The lack of a clinically relevant effect of grapefruit juice on sunitinib exposure was not related to the batch of grapefruit juice that was used in this study. First, the grapefruit juice selected had a sufficient content of BG (2.2mg/ 1.6mg) to induce a significant effect on CYP3A4 activity.[15] Secondly, even after the recovery of a proportion of the intestinal CYP3A4 enzymes on the second PK day, a significant effect ~50% was observed on the phenotypic drug midazolam, which is comparable to the effect of grapefruit juice on midazolam exposure explored in earlier interaction studies[25, 40]. No effect of sunitinib on midazolam exposure is expected since midazolam exposure is similar to earlier published data[40, 42]. The increase in midazolam exposure due to grapefruit juice co-administration confirms the significant effect that grapefruit juice has on intestinal CYP3A4 activity. Hence, the marginal effect observed on sunitinib bioavailability is likely to be the result of the limited efficiency of sunitinib metabolism by intestinal CYP3A4. The limited effect of grapefruit juice is in contrast with the large effect (51% increase) observed after the co-administration of ketoconazol.[3] This could be the result of a change in enzymes that play a dominant role after prolonged exposure to the drug as was seen for imatinib in earlier studies.[43] The interaction with ketoconazol was studied after a single dose, while the interaction with grapefruit juice was determined at steady-state sunitinib exposure. Another explanation could be that ketoconazol is a strong intestinal and hepatic CYP3A4 inhibitor while grapefruit juice is only capable of inhibiting intestinal CYP3A4.

In conclusion, grapefruit juice only marginally increases the sunitinib exposure which is not regarded clinically relevant. Therefore, the warning in the drug label for the concomitantly use of grapefruit juice should be reconsidered.

Acknowledgement

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