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The influence of green tea extract on nintedanib's bioavailability in patients with pulmonary fibrosis

G.D.Marijn Veerman [a,*], Sanne C. van der Werff [a], Stijn L.W. Koolen [a,b], Jelle R. Miedema [c], Esther Oomen-de Hoop [a], Sophie C. van der Mark [c], Prewesh P. Chandoesing [c], Peter de Bruijn [a], Marlies S. Wijsenbeek [c], Ron H.J. Mathijssen [a]

[a] Dept. of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
[b] Dept. of Hospital Pharmacy, Erasmus MC, Rotterdam, The Netherlands
[c] Dept. of Pulmonology, Erasmus MC, Rotterdam, The Netherlands

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ABSTRACT

Nintedanib is an oral small-molecule kinase inhibitor and first-line treatment for idiopathic pulmonary fibrosis. Nintedanib is a substrate of the drug efflux transporter ABCB1. Green tea flavonoids –especially epigallocatechin gallate (EGCG)– are potent ABCB1 modulators. We investigated if concomitant administration of green tea extract (GTE) could result in a clinically relevant herb-drug interaction.

Patients were randomized between A-B and B-A, with A being nintedanib alone and B nintedanib with GTE. Both periods lasted 7 days, in which nintedanib was administered twice daily directly after a meal. In period B, patients additionally received capsules with GTE (500 mg BID, >60% EGCG). Pharmacokinetic sampling for 12 h was performed at day 7 of each period. Primary endpoint was change in geometric mean for the area under the curve ($AUC_{0-12\ h}$). A linear mixed model was used to analyse AUCs and maximal concentration (C_{max}).

In 26 included patients, the nintedanib $AUC_{0-12\ h}$ was 21% lower (95% CI −29% to −12%; $P < 0.001$) in period B (with GTE) compared to period A. C_{max} did not differ significantly between periods; − 14% (95% CI −29% to +4%; $P = 0.12$). The detrimental effect was predominant in patients with the *ABCB1* 3435 C>T wild type variant. No differences in toxicities were observed.

Exposure to nintedanib decreased with 21% when administered 60 min after GTC for only 7 days. This is a statistically significant interaction which could potentially impair treatment efficacy. Before patients and physicians should definitely be warned to avoid this combination, prospective clinical validation of an exposure-response relationship is necessary.

1. Introduction

Nintedanib is a multi-target small-molecule kinase inhibitor (SMKI) and used in the treatment of various lethal pulmonary diseases. Initially, this drug was developed to treat metastatic non-small cell lung cancer and hence obtained its current registration as a second-line treatment concomitant with docetaxel [1]. Today however, nintedanib's main registration is as first-line monotherapy for idiopathic pulmonary fibrosis (IPF) [2,3]. IPF is an orphan disease, with a prevalence and incidence of 28 and 17 patients per 100.000 people, respectively [4]. Patients with IPF have a median survival of 3–4 years when untreated [5]. Because nintedanib inhibits multiple pathways which cause progression of pulmonary fibrosis, treatment results in a significant decrease in the decline of pulmonary function, less exacerbations [3,6] and improved survival [7]. Most recently, nintedanib was additionally approved as treatment for other progressive fibrotic interstitial lung diseases (ILD) [8].

A majority of patients using nintedanib experience adverse events. The most common toxicities of nintedanib are diarrhoea (> 60%), nausea (> 22%), vomiting (> 12%) and elevated liver enzymes [1–3,9]. More than 30% of patients experience serious adverse events during treatment [3]. Nintedanib is advised to be administered concomitantly with food, because then its absorption is increased by 20% and fewer side effects are experienced [2,10].

* Correspondence to: Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.
E-mail address: g.veerman@erasmusmc.nl (G.D.Marijn Veerman).

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Unfortunately, the absolute bioavailability of nintedanib is low to approximately 4.7% and it is metabolized by CYP3A4. Well known drug-drug interactions with CYP-enzyme inhibitors or inducers are therefore not likely [11]. However, since nintedanib is orally administered, its inter- and intrapatient variability are moderate to high [1,2]. This could partly be due to drug-drug interactions, life style, race, and food-drug interactions [10,11]. Additionally, nintedanib is a substrate for the drug efflux transporter P-glycoprotein (ABCB1) [1,2,11]. ABCB1 is present in the gastro-intestinal tract and blood-brain barrier [12]. It plays a key role in active cellular drug excretion *c.q.* reducing absorption and increasing excretion, which results in a lower drug exposure. The *ABCB1* single nucleotide polymorphism (SNP) 3435 C>T, which is frequently present in the general population (24% homozygote), significantly reduces intestinal ABCB1 activity and digoxin bioavailability [13]. The activity of ABCB1 can also be altered by flavonoids [12,14], especially by epigallocatechin gallate (EGCG) [15–17]. ECGC is highly concentrated in the popular beverage green tea [15–17]. Green tea extract has shown to decrease drug concentrations of digoxin in patients, but this has never been studied in patients treated with SMKIs [10,18]. This effect was seen after single-dosing and multiple-dosing of green tea extract [18]. An explanation for this effect could be pharmacologic induction of ABCB1. Potentially, concomitant green tea usage leads to altered nintedanib absorption or excretion in the gastro-intestinal tract, which subsequently alters nintedanib's absolute bioavailability. When this effect is large, treatment efficacy or toxicity could be altered too. Furthermore, patients treated for pulmonary fibrosis of various etiologies can be treated with various other drugs that may interact with both nintedanib and green tea. Hence it is important to confirm potential interactions which are found *in vitro*, by studying these interactions *in vivo*.

Based on the European Food and Safety Authority's scientific opinion, 300 mg of EGCG is considered the general daily intake from consumption of green tea, which increases to 866 mg EGCG/day for high-level consumers [19]. A dosage of 300 mg EGCG is comparable to 700 mL (5–6 cups daily) of green tea [20]. In most labels of green tea extract capsules it is advised to take –at least– twice this dosage [21], up to 1000 mg EGCG/day [19]. Additionally to the regular use of green tea as beverage, more concentrated green tea extracts are being used as alternative (prophylactic) medicine for various diseases [22], including COVID-19 [23]. Specifically for IPF, EGCG showed different expression of fibroblastic micro RNA *in vitro* and further studies in patients were advised [24].

To date, the effects of green tea (extract) on the pharmacokinetics of any SMKI have never been studied in humans. We thus aimed to study the interaction between nintedanib and green tea extract with > 60% ECGC in patients with fibrotic ILD. Depending on the presence and magnitude of the interaction, we aimed to give practical recommendations for daily practice to physicians and patients.

2. Methods

2.1. Patient selection

Adult patients treated with nintedanib for any fibrotic ILD were eligible for study participation if they did not use, or could abstain from, strong ABCB1 and/or CYP3A4 interacting drugs or alternative compounds (including green tea). Daily treatment with a stable dosage of nintedanib for two weeks was mandatory to minimize the chance of dose reductions because of toxicity during the study period. Patients were allowed to use proton-pump inhibitors, low-dose steroids (prednisone ≤10 milligrams) and other anti-inflammatory drugs which did not interact with nintedanib (*e.g.* mycophenolic acid, methotrexate, or rituximab). There drugs had to be continuously used during both study periods. All patients had to provide written informed consent prior to start. The blood withdrawal for pharmacogenetic analysis was optional. The Erasmus University Medical Center Rotterdam ethics committee approved this study (MEC 20–558) and it was registered in the Dutch Trial Registry (www.trialregister.nl; NL8913).

2.2. Study design

This was a randomized, two-period cross-over pharmacokinetic study, with the concomitant use of green tea extract as the intervention. Patients were computer-randomized by an independent trial bureau in blocks of four patients. The study design is presented in Fig. 1. Every patient participated in two periods of seven study days each to guarantee steady state concentrations: control period (A) and intervention period (B). In both periods, nintedanib (Boehringer Ingelheim) was taken twice daily with water, directly after a standardized breakfast –one or two slices of bread with cheese or ham– in the morning and after a low-fat diner in the evening. The intervention in period B included the concomitant use of 500 mg green tea extract (*Camellia sinensis,* House of Ingredients NV, Wetteren, Belgium, batch CP20200201) with 60.70% EGCG, taken twice daily with 250 mL water, 30 min prior to the meals. Hence, there was approximately one hour between the administrations of the green tea extract and nintedanib. At the last day of each period, patients were admitted for 12 h pharmacokinetic sampling at t = 0 h, t = 0.5 h, t = 1 h, t = 1.5 h, t = 2 h, t = 2.5 h, t = 3 h, t = 3.5 h, t = 4 h, t = 5 h, t = 6 h, t = 8 h and t = 12 h. During both admissions, nintedanib was taken following the exact same breakfast (one or two slices of bread with cheese or ham). Free intake of other food or beverages was prohibited from two hours prior until one hour after nintedanib administration. In period B, the green tea extract was administered with 250 mL water, 30 min prior to the breakfast. To prevent any carry-over interference of green tea extract from period B in period A, a wash-out period of 14 days was designed in arm 2. The plasma samples of every patient were quantified in the same run by a robust liquid chromatography-tandem mass spectrometric assay [25]. With these nintedanib plasma concentrations in ng/mL, Area Under the plasma concentration Curve for 12 h ($AUC_{0-12\ h}$), maximum concentration (C_{max}), time to C_{max} (T_{max}) and half-life (T_{half}) were calculated using WinNonlin software, Phoenix, version 8.3.

The *ABCB1* SNP 3435 C>T was determined by digital-droplet polymerase chain reaction (ddPCR) from a full-blood sample which was withdrawn during the study period. Since the 3435 C>T SNP is a germline variant, date and time of blood withdrawal was not important.

2.3. Study end points

The primary study objective was the difference in geometric mean $AUC_{0-12\ h}$ of nintedanib between the periods with and without using green tea extract. Secondary study objectives were differences in other pharmacokinetic parameters (*i.e.* C_{max}, T_{max} and T_{half}). Additionally, the influence of the *ABCB1* SNP 3435 C>T on the interaction was investigated. Finally, the influence of green tea extract on adverse events was compared.

2.4. Protocol compliance and adverse event monitoring

To monitor study protocol adherence, patients were provided with a diary to report the exact times and manner of all the administrations of nintedanib and green tea extract during the study periods. Additionally, patients were asked to report any new or ongoing adverse events. Adverse events were also systematically scored at the two hospital admissions by the investigating physician according to the Common Terminology Criteria for Adverse Events grades version 5.0 [26].

2.5. Statistical analyses

A relative difference in $AUC_{0-12\ h}$ of minus 20% or plus 25% is considered to be clinically relevant by both U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) [27,28].

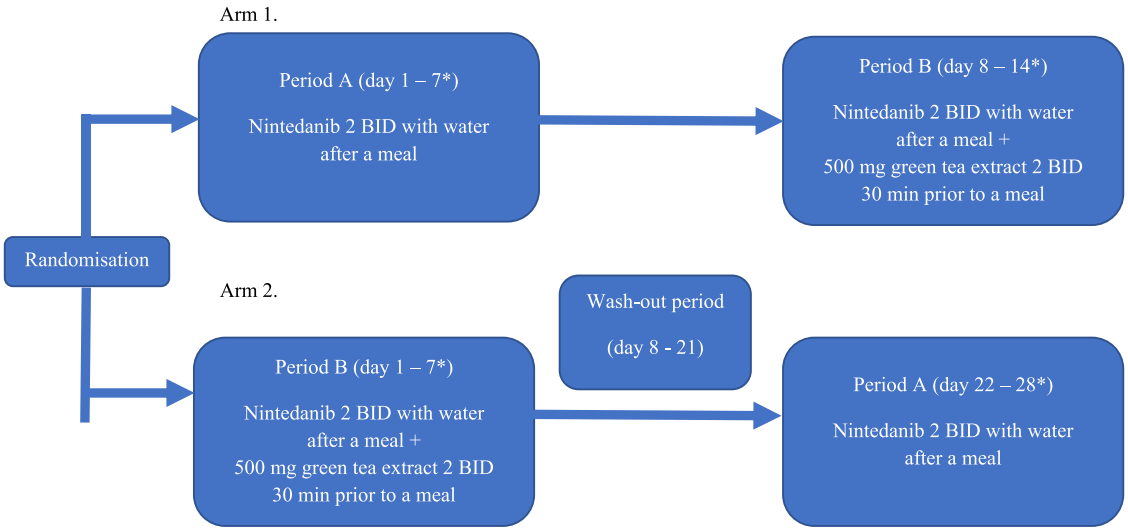

Fig. 1. Study design. Nintedanib was taken 2 BID (twice daily) with 250 mL of water directly after a meal. In period B, 500 mg green tea extract was administered with 250 mL of water at 30 min prior to the same meals. Hence, time between intake of the green tea extract and nintedanib was approximately 1 h.

For sample size calculation, the within-patient standard deviation was assumed to be 30% [29], and the two-sided α is set at 5%, which lead to a total of 26 evaluable patients (13 in both treatment arms) being required to detect a difference with 90% power [30].

All statistical analyses of $AUC_{0–12\,h}$ and C_{max} were performed on a log-transformed scale, assuming they follow a log-normal distribution [31]. Linear mixed effect modelling was performed for the mean differences in (log) $AUC_{0–12\,h}$ and C_{max} with treatment, sequence, and period as fixed effects and subject within sequence as a random effect [32]. Variance components were estimated by restricted maximum likelihood (REML) methods, and the Kenward-Roger method was used to compute the degrees of freedom of the denominator. $AUC_{0–12\,h}$ and C_{max} mean differences including 95% confidence intervals (CIs) were exponentiated to provide point estimates of the ratios of geometric means and their 95% CIs (*c.q.* relative differences). T_{max} was compared using the Wilcoxon signed rank test. The influence of the *ABCB1* 3435 C>T SNP on the effect of green tea extract was explored with a Mann-Whitney *U* test, assuming the differences in AUC were not normally distributed. The incidence and severity of adverse events were reported of each period separately. The study was not powered to detect a statistically significant difference for this endpoint, thus these results were of a descriptive nature. Statistical analyses were performed with Stata (StataCorp. 2020. Stata: Release 16.1. Statistical Software. College Station, TX: StataCorp LP).

3. Results

3.1. Patients

Between October 2020 and November 2021, 28 patients were included in the study. Two patients were not evaluable due to protocol violations: one patient took the nintedanib too early and the other took nintedanib without the prescribed standardized breakfast. There were no changes in co-medication during the study period. The most used anti-inflammatory co-medication in our study population were low-dose steroids (31%), mycophenolic acid (15%) and rituximab (4%). Table 1 presents all evaluable patients' demographics. None of the participants were current smokers.

3.2. Pharmacokinetic effects of green tea extract

The use of green tea extract resulted in a statistically significant decrease of 21% (95% CI −28.7% to −12.1%) in geometric nintedanib mean $AUC_{0–12\,h}$. The decrease in exposure was seen in 21 (81%) of the total 26 patients, while 13 patients (50%) decreased at least 20% in $AUC_{0–12\,h}$. Fig. 2 shows the two plasma concentration-time curves of nintedanib in the periods with and without green tea extract. The difference in $AUC_{0–12\,h}$ was not apparent in the first -absorption- part of the curve, but the concentration-time profiles begin to separate after five

Table 1
Patient demographics.

Demographic	Total included (n = 28)
Sex	
Male	22 (79%)
Female	6 (21%)
Age (years) median [IQR]	68.5 [60–73]
Fibrosing ILD	
Interstitial pulmonary fibrosis	10 (36%)
Fibrotic non-specific interstitial pneumonia	7 (25%)
Familiar pulmonary fibrosis	5 (18%)
Hypersensitivity pneumonitis	3 (11%)
Unclassified	2 (7%)
Usual interstitial pneumonia	1 (4%)
Forced vital capacity	
Median (mL) [IQR]	2455 [1942.5–3185]
Median % of predicted [IQR]	69.5 [51.75–82.50]
Diffusing capacity for carbon monoxide	
Median (mmol/min/kPa) [IQR]	3.27 [2.44–4.61]
Median % of predicted [IQR]	42 [30–52]
Race	
Caucasian	24 (86%)
Black	3 (11%)
Asian	1 (4%)
PPI use	
Yes	19 (68%)
No	9 (32%)
Nintedanib dose	
150 milligrams BID	18 (64%)
100 milligrams BID	8 (29%)
100 + 150 milligrams*	2 (7%)

Abbreviations: n = number of patients; IQR = interquartile range; ILD = interstitial lung disease; mL = millilitres; mmol = milimole; min = minute; kPa = kilopascal; PPI = proton-pump inhibitor. * = patients who were dosed 100 milligrams QD every morning and 150 milligrams QD every evening.

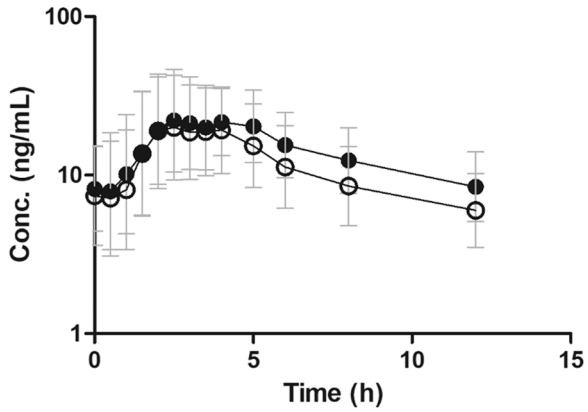

Fig. 2. Plasma concentration curves of nintedanib with and without green tea extract.
The lines represent the geometric mean concentrations of nintedanib when taken in phase A without (black dots) and phase B with (blank dots) green tea extract. The grey error bars represent the standard deviation.

hours. Interpatient variability (coefficient of variation) in $AUC_{0–12\,h}$ decreased with GTC from 57% to 42%. Other pharmacokinetic parameters -C_{max}, T_{max} and T_{half}- were not statistically significantly influenced by green tea extract. All these pharmacokinetic results are depicted in Table 2.

3.3. Influence of ABCB13435 C>T on the effect of green tea extract

All 26 patients provided additional informed consent for pharmacogenomic analysis of the *ABCB1* polymorphism. In 100% of patients, the ddPCR analysis was successfully performed. Ten patients were wild type (CC), 13 patients were heterozygote variant (CT) and 3 patients were homozygote variant (TT) for this mutation. The effect of green tea extract was significantly larger in wild type patients compared to heterozygote variant patients (−27% versus −9%; p = 0.025). However, in a dominant model (CC versus CT + TT) the Mann-Whitney *U* test was not statistically significant any more (p = 0.065; Fig. 3).

3.4. Toxicity

Table 3 presents the incidence and severity of all experienced adverse events during the study period. No serious adverse events occurred as a result of the herb-drug combination. In period B compared to period A, no additional study intervention-related adverse events were apprehended. In five patients, gastro-intestinal toxicity decreased (39% versus 28% diarrhoea and 14% versus 7% nausea). In most patients however, no difference in adverse events was seen.

Table 2
Pharmacokinetic results per period.

Pharmacokinetic parameter	Without green tea extract (n = 26)	With green tea extract (n = 26)	RD with versus without green tea extract (95% CI)	P-value
Nintedanib				
$AUC_{0–12\,h}$ (CV %) geomean μg*h/mL	167.7 (57.1%)	132.8 (41.6%)	-20.8% (−28.7% to −12.1%)	< 0.001
C_{max} (CV %) geomean μg/mL	33.5 (66.3%)	28.9 (59.6%)	-13.8% (−28.6% to 4.1%)	0.118
T_{max} (IQR) median hours	2.50 (1.50–3.98)	2.50 (2.00–3.98)	NA	0.869
T_{half} (IQR) median hours	5.60 (4.62–7.92)	7.19 (5.10–11.3)	NA	0.131

Abbreviations: $AUC_{0–12\,h}$ = Area under the plasma concentration curve, time 0–12 h; CI = Confidence Interval; RD = relative difference; Cmax= maximum concentration; CV = coefficient of variation; h = hours; n = number of patients; T_{max} = time until maximum concentration; IQR = interquartile range; T_{half} = half-life; NA = not applicable.

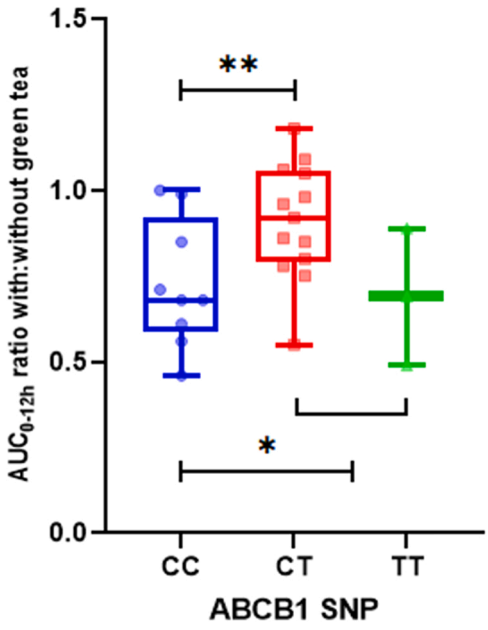

Fig. 3. The influence of *ABCB1* 3435 C>T on the effect of green tea extract.The box plots show the median $AUC_{0–12\,h}$ ratio with ranges in effect of green tea extract on the exposure of nintedanib (Y-axis) between *ABCB1* 3435 C>T wild type (CC), heterozygote variants (CT) and homozygote variants (TT). * p = 0.025; * * p = 0.065.

Table 3
Incidence and severity of adverse events.

	Phase A (n = 26)		Phase B (n = 26)	
Adverse event	Grade 1	Grade 2	Grade 1	Grade 2
All events	19 (68%)	6 (21%)	19 (68%)	6 (21%)
Reported in ≥ 5% of patients				
Diarrhoea	9 (32%)	2 (7%)	6 (21%)	2 (7%)
Nausea	4 (14%)	–	2 (7%)	–
Dyspnoea	3 (11%)	3 (11%)	2 (7%)	3 (11%)
Pain	3 (11%)	1 (4%)	2 (7%)	1 (4%)
Anorexia	3 (11%)	1 (4%)	3 (11%)	1 (4%)
Fatigue	1 (4%)	1 (4%)	2 (7%)	–
Rash	2 (7%)	–	2 (7%)	–
Cough	–	–	2 (7%)	–
Serious adverse event	–	–	–	–

Adverse events of all evaluable patients per phase. Adverse events were scored by the Common Terminology Criteria for Adverse Events grades version 5.0 [26]. Phase A = seven days nintedanib intake without green tea extract. N = number of patients. Phase B = seven days nintedanib intake one hour after green tea extract.

4. Discussion

This is the first study to report a significant decrease in nintedanib exposure when administered with green tea extract in patients with fibrotic ILD. This decrease is clinically relevant according to FDA guidelines and could impair treatment efficacy. Hence, we advise to be cautious with the concomitant use of green tea extract capsules or large

consumption of green tea for patients using nintedanib.

Until now, only two *in vivo* studies with green tea extract and SMKIs were performed in rats. Both studies showed vast decreases of 51–74% in exposure of the SMKIs erlotinib, lapatinib and sunitinib [33,34]. The results of our study are in line with these findings, although the magnitude is smaller. This could be because these rats were treated with much higher concentrations of green tea extract compared to our study. Another explanation could be that green tea flavonoids are potent inducers of both ABCB1 and CYP3A4. Erlotinib, lapatinib and sunitinib are all three largely metabolized by CYP3A4, but nintedanib is only for a minority metabolized by this enzyme [11].

The green tea extract dosage we used in this study corresponds with twice the normal dosage of EGCG according to the EMA, and is around two-third of the maximal safe EGCG daily dosage [19]. The study dose is similar to the consumption of approximately 1.4 litres (10–12 cups) of green tea [20] and is a common daily dose of over the counter capsules of green tea [19,21]. Therefore, we advise patients and physicians to avoid green tea extracts and to be cautions with high amounts of green tea beverage. Whether or not lower dosages of EGCG will have the similar effect on the exposure to nintedanib is unknown. A recent study on the effect of green tea extract on tamoxifen, an antagonist of oestrogen used in the treatment of hormone-sensitive breast cancer, demonstrated green tea dosage is relevant. With half the EGCG dose, no significant effect on drug exposure was found [35]. Moreover, *in vitro* studies mostly found an opposite effect of EGCG on ABCB1 [14–17]. For example, in the presence of EGCG, ABCB1 expression in cell lines was decreased by 75% [17]. Moreover, a dose-dependent effect of green tea resulted in complete inhibition of digoxin basal to apical cell membrane translocation [15]. Hence, modest green tea consumption could be safe, but higher doses of green tea (extract) should be avoided in order to prevent any harmful interaction.

Pharmacokinetic induction of enzymes and transporters is a relatively slow process, because extra proteins must be produced to overexpress [36]. On average, the maximal inducing effect is reached after one to two weeks [37]. Hence, the decrease in exposure could be larger if the green tea extract was used for multiple weeks. The effect of induction does therewithal last longer than inhibition does. Hence, the additional two weeks wash-out were also important to (partly) normalize ABCB1 and CYP3A4 expression after one week of green tea extract consumption. Nevertheless, the here found effect could still be underestimated.

Although green tea extract caused the exposure of nintedanib to clinically relevant decrease according to FDA guidelines [28], the true clinical relevance on nintedanib efficacy in clinical practise is yet unknown. There is evidence that a higher nintedanib dose increases efficacy in terms of the annual rate of decline in FVC for the patients dosed with 150 mg BID compared to 100 mg BID or lower [38]. However, there is no known plasma target concentration for efficacy, nor has any large prospective study investigated the exposure-response relationship in interstitial lung disease patients. When a plasma target concentration for efficacy has been found, the results of this study can be placed in this broader context.

Furthermore, no (large) difference in reported adverse events was seen. This might be related to the limited exposure time to the green tea extract. Moreover, there is no well-studied relationship between exposure and toxicity of nintedanib; only a dose-toxicity relationship was observed [38,39]. Hence, it could be that the found decrease in $AUC_{0-12\,h}$ was not large enough to result in a clear decrease in toxicity as well. Additionally, green tea extract itself could cause new or increased (mostly gastro-intestinal) adverse events too.

The interaction between nintedanib and green tea extract is probably based on induction of the efflux transporter ABCB1. This could explain the characteristic $AUC_{0-12\,h}$ curve in Fig. 2 with increased excretion. Therefore, it may be that the detrimental effect of green tea extract was predominantly seen in patient with a wild type ABCB1 transporter. In patients with the 3435 C>T germline polymorphism, the effect was smaller. Nevertheless, since this analysis was merely explorative, these results should be validated. The current findings do underline the clinical importance of the efflux transporter ABCB1 in the treatment of nintedanib. If the presence of germline mutations in ABCB1 are clinically relevant for the treatment with nintedanib, is currently unknown. In patients with non-small cell lung cancer, which are treated with other SMKIs, multiple variants are correlated with treatment effect or toxicity [40]. Hence the broader effect of this polymorphism needs further studying.

Concomitant use of potent modulators of ABCB1 –ketoconazole and rifampicin– altered nintedanib exposure and should be administered with caution [2,11]. Since we here additionally show the potent effects of green tea flavonoids, other sources of flavonoids could be potential interacting too. EGCG concentrations in different types of tea largely vary. White tea has, compared to green tea, similar levels of EGCG and total catechins [41,42]. Hence, the interaction with green tea could be extrapolated to white tea. Red and black tea however do not have detectable concentrations of EGCG, but a comparable amount of other catechins [42]. These latter differences have clinical relevance, if EGCG is the definite interacting compound in green tea (extract). Then, there may be the possibility to advise patients and physicians the use of red and black teas instead of green and white teas. Flavonoids (*c.q.* antioxidants) are also present in high concentrations in red wine and cacao [43]. Before we advise to discourage the use of all these foods and drinks, proper studies to their true effect should be performed first. The use of supplements with these compounds should however be avoided.

The limitations of this study revolve around the lack of quantification of green tea flavonoids in the plasma of the participants. Quantification of EGCG could help relate systemic concentrations with the magnitude of the observed effect. Furthermore, it would help to know how long green tea compounds are present in the blood, so further studies could be designed with a longer or shorter wash-out period. However, future studies to this green tea effect should take into account the slow inducing effect of green tea extract. Hence it should be considered using green tea for a longer period of time. A longer wash-out period would not be necessary, since no sequence effect was observed between the two randomisation arms (data not shown).

To conclude, exposure to nintedanib significantly decreased with 21% when administered 60 min after green tea extract BID for 7 days. Green tea extract probably caused induction of ABCB1. This is a clinically relevant interaction which could potentially impair treatment efficacy. The results of this study could therefore indicate that large consumption of green tea or green tea extract should be avoided by patients using nintedanib. Before patients and physicians should definitely be warned to avoid this combination, prospective clinical validation of an exposure-response relationship is necessary.

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Ethics approval

The study was approved by the local ethics committee (Erasmus University Medical Center Rotterdam; MEC 20-558) and was registered in the Dutch Trial Registry (www.trialregister.nl; number NL8913).

CRedit authorship contribution statement

GDMV wrote the manuscript. GDMV, MSW, JRM, SLWK, and RHJM designed the research. GDMV, SCW, MSW, JRM, SCM, and PPC performed the research. GDMV, SCW, EOdH, SLWK, PdB, and RHJM analysed the data. PdB contributed new reagents and analytical tools.

Data Availability

Preliminary data of this study have been presented during an oral session at the 19th International Congress of Therapeutic Drug Monitoring & Clinical Toxicology (IATDMCT, Rome, September 19-22, 2021). The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

G.D. Marijn Veerman reports grants from Eli Lilly; outside the submitted work. Jelle R. Miedema reports grants from Boehringer Ingelheim, Novartis and Hoffman la Roche; outside the submitted work. Marlies S. Wijsenbeek reports grants from Boehringer Ingelheim, Hoffman la Roche; consulting fees from Boehringer Ingelheim, Hoffman la Roche, Galapagos, Bristol Myers Squibb, Galecto, Respivant, Nerre Therapeutics; Lecture fees from Boehringer Ingelheim, Hoffman la Roche, Novartis; travel support from Boehringer Ingelheim, Hoffman la Roche; Participation in data safety monitoring boards Savara, Galapagos. All grants and fees were outside the submitted work (paid to institution). Ron H.J. Mathijssen reports grants from Servier, Sanofi, Boehringer-Ingelheim, Bayer, Astellas, Pamgene, Cristal Therapeutics, Pfizer, Novartis and Hoffman-La Roche; outside the submitted work (paid to institution). All other authors declare no competing interests.

Consent to participate

All participating patients were asked to sign a written informed consent form prior to participation.

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