Clinical pharmacology of the tyrosine kinase inhibitors imatinib and sunitinib

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Effect of cigarette smoking on pharmacokinetics, safety and efficacy of imatinib: a study based on data of the Soft Tissue and Bone Sarcoma Group of the EORTC

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Abstract

Purpose: Smoking is a potent inducer of cytochrome *P*450 (CYP) 1A2 and may affect the pharmacokinetics of CYP1A2 metabolized drugs. The effect of smoking on the pharmacokinetics of imatinib, which is metabolized by CYP3A4 and partly by CYP1A2, is unknown. We studied the effect of smoking on imatinib pharmacokinetics, safety, and efficacy.

Experimental Design: Imatinib pharmacokinetics, safety, and efficacy were analyzed in 45 patients with gastrointestinal stromal tumors (GIST) or soft-tissue sarcoma included in two European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trials, including 15 smokers and 30 nonsmokers. Apparent oral clearance, distribution volume, elimination half-life, and dose-standardized area under the concentration curve (AUC) were assessed in 34 patients using nonlinear mixed-effect modeling.

Results: Mean ± SD pharmacokinetic variables in smokers (n = 9) versus nonsmokers (n = 25) groups were 9.6 ± 5.5 versus 9.2 ± 4.6L/h (apparent oral clearance), 216.5 ± 114.3 versus 207.0 ± 116.9 L (distribution volume), 16.1 ± 6.0 versus 16.5 ± 6.0 h (elimination half-life), and 133.6 ± 71.0 versus 142.3 ± 84.0 ng·h/mL·mg area under the concentration curve; $P > 0.05$. Smokers experienced more grade 2/3 anemia ($P = 0.010$) and fatigue ($P = 0.011$) and those with GIST had a significantly shorter overall survival ($P = 0.037$) and time to progression ($P = 0.052$).

Conclusions: This retrospective study suggests that the pharmacokinetics of imatinib is not affected by smoking. However, smokers have an increased risk of anemia and fatigue. Smokers with GIST have a shorter overall survival and time to progression.

Introduction

Tobacco smoking is a major problem for public health[i]. Despite all the attention paid to the negative effects of smoking cigarettes by the medical profession and media, its prevalence remains high[ii]. Between 2002 and 2005, ~ 34% and 23% of men and women, respectively, smoked in the European Union[iii]. The smoking prevalence in the United States is similar, with estimates of 24% to 32% of men and 18% to 21% of women smoking[1]. Among the various biological effects, tobacco smoke induces several drug-metabolizing enzymes. One of the constituents in tobacco smoke known to be involved in the induction of cytochrome P450 (CYP) 1A1, 1A2, 2E1 and UDP-glucuronosyltransferases are the polycyclic aromatic hydrocarbons, a product of incomplete combustion of organic matter[2]. CYP1A1 and CYP1A2 are involved in the metabolism of a variety of drugs. By inducing these CYPs, smoking can interfere with the pharmacokinetics of many drugs. The most extensively described pharmacokinetic interaction between smoking and drug clearance is that of clozapine, which is primarily metabolized by CYP1A2[3-5]. However, in addition, the metabolism of drugs that are not predominantly metabolized by CYP1A2 can be influenced by smoking. For example, erlotinib is principally metabolized by CYP3A4 and to a minor extent, by CYP1A2. Smoking has been shown to increase the clearance of erlotinib by 23.5% and may therefore reduce the efficacy of the drug in patients with non-small-cell lung cancer[6]. Likewise, imatinib, also a receptor tyrosine kinase inhibitor, is principally metabolized by CYP3A4 and CYP3A5 with CYP1A1, CYP1A2, CYP2C9, CYP2C19, and CYP2D6 playing a secondary role[7, 8]. However, the role of CYP3A4 in imatinib metabolism is under discussion since acute inhibition of CYP3A4, by the potent CYP3A4 inhibitor ritonavir, did not result in a substantial change in the PK of imatinib at steady-state exposure levels [8]. This might be a result of the activity of other CYP enzymes, which while playing only a secondary role in *in vitro* experiments become the principal catabolic enzymes when the main metabolic route is blocked. Induction of an enzyme that only plays a secondary role in the metabolism of imatininb might likewise result in a shift in importance of the individual CYPs.

Therefore, we aimed to explore the effect of smoking on the pharmacokinetics of imatinib as a primary endpoint and the effect of smoking on adverse events and treatment outcome as secondary endpoints.

i European Commission. Tobacco and Health in the European Union. Visited Sept 2007 http://ec.europa.eu/health/ph_determinants/life_style/Tobacco/Documents/tobacco_fr_en.pdf

ii Lopez AD, Collishaw N.E., Piha T.A. Tobacco Control Country Profiles. Visited Sept 2007 http://www.who.int/tobacco/statistics/country_profiles/en/Introduction.pdf

iii World Health Organization. Tobacco control database; Adults. Visited Sept 2007 http://data.euro.who.int/tobacco/

Materials and methods

Patients and treatment

A total of 91 patients were included in 2 European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group phase I and II trials of imatinib in patients with gastrointestinal stromal tumors (GIST) and other soft-tissue sarcomas[9-11]. Smoking data were only available for 45 patients; pharmacokinetic data were available for 34 of these patients. The patients from three centers (Leuven, Belgium; London, United Kingdom; and Rotterdam, The Netherlands) were included in this retrospective analysis[9-12]. Eligible patients had histologically proven soft-tissue sarcomas, and those with GISTs were required to be KIT positive by CD117 expression on immunohistochemical staining. Patients had to have a measurable lesion with evidence of progression of < 6 weeks before treatment. Previous chemotherapy was allowed, but had to be discontinued for at least 4 weeks. Additional s elected eligibility criteria for inclusion were WHO performance status of ≤ 2; adequate haematological, renal, and hepatic function; no other severe illness; and no concomitant use of coumarin, other investigational drugs, or systemic corticosteroid therapy; before patient registration, written informed consent was given according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/European Union-Good Clinical Practice and national-local regulations.

Patients were treated with imatinib 400 mg once daily (7 patients), 300 mg twice daily (7 patients), 400 mg twice daily (25 patients), or 500 mg twice daily (6 patients). All toxicities were graded using the National Cancer Institute Common Toxicity Criteria version 2.0.

Smoking status

Patients were categorized as smokers or non-smokers based on information collected and recorded before study entry. If the smoking behavior was not clearly described in the medical record, the patients were excluded from analyses. In the *de novo* analysis, we divided the patients in two groups: ever versus never smokers. The rationale for this is that it is unclear for how long after cessation smoking could influence the toxicity profiles and overall survival as well as other clinical endpoints such as time to progression. In contrast, with regard to alteration of pharmacokinetic variables by smoking, the *a priori* hypothesis is that smoking induces CYP1A2. In that case, it is clear that the influence of smoking will last for a maximum of 9 days, because the half life of CYP1A2 is estimated to be ~ 38.6 h after smoking cessation[13]. In the sensitivity analysis, we have studied the possible effect of the two different ways of categorization and repeated the analysis with the criterion of current smokers. In fact, two patients who were classified as ever smokers stopped smoking >1 year before imatinib therapy started. This analysis showed that the two different ways of categorization did not alter the outcome of the statistics (the association remained not significant).

Pharmacokinetic Analysis

Blood samples were taken for pharmacokinetic analysis as described in the phase I and II studies. On day 1 blood samples were taken pre-dose, and 1, 2, 3, 4, 8, 12, 14 and 24 h after dosing for patients receiving one daily dose. For patients being dosed twice daily, the 12 h sample was taken after the first dose, just before the second dose, and the 14 h sample 2 h after the second dose. In both groups of patients, the 24 h sample was before the second and the third dose of imatinib respectively[9, 11].

The plasma imatinib concentrations were determined in the Novartis USA bioanalytical laboratory using a validated liquid chromatography-tandem mass spectrometry assay[14].

The pharmacokinetic variables were estimated with a one-compartment model with zero-order absorption and first-order elimination. The model was developed with nonlinear mixed-effect modeling in the study of Judson et al. The following pharmacokinetic variables were estimated: volume of distribution (V_d), apparent oral clearance (Cl/F), elimination half life ($t_{1/2}$), and absolute and dose-standardized area under the concentration time curve (AUC). Details on the model can be found in the original article[12].

Statistics

The estimated pharmacokinetics variables were compared between the smoker and non-smoker populations using the Student's *t*-test. The maximum grades of observed toxicities were compared between those populations using a Cochrane-Armitage χ^2 test for trend; if this test was significant, the probability of undergoing a grade ≥ 2 toxicity was analyzed in a logistic model including the initial imatinib daily dose and the smoking status; if this test was significant, the probability of undergoing a grade ≥ 2 toxicity was analyzed in a logistic model stratified by imatinib daily dose. The time to progression and overall survival were compared between smokers and non-smokers using the log-rank test. All statistical tests were done two-sided with rejection of the null hypothesis at $P < 0.05$. All statistical analyses were performed using SAS, version 9.1 for Windows (SAS Institute). The sample size was based on the available data. A retrospective power computation shows that the study had a 69% power to detect a 50% elevation of the Cl/F calculated with a two-sided *t*-test and a 62% power to detect a 50% decrease of the dose-standardized AUC.

Results

Smoking data were available for 45 patients and pharmacokinetic data for 34 of these. Therefore, correlation of the smoking status with pharmacokinetics, the primary endpoint, is based on the analysis of 34 cases, whereas the correlation of the smoking status with treatment outcome, the secondary endpoint, is based on 45 patients. In the group of

45 patients with smoking data 15 patients were categorized as smokers and 30 were categorized as non-smokers. The patient characteristics and the distribution of the smokers and the non-smokers over the different treatment arms are listed in Tables 1 and 2.

Table 1 Patient characteristics

	Smokers (n=15)	Non-smokers (n=30)	Total (n=45)
Sex			
Male	10	18	28
Female	5	12	17
Age group			
<40	3	5	8
40-50	2	9	11
50-60	7	9	16
60-70	3	7	10
Weight			
Median (range)	77.0 (46.2 - 104.7)	70.3 (30.6 – 102.2)	70.4 (30.6 – 104.7)
Prior chemotherapy			
No	6	15	21
Yes	9	15	24
GIST			
No	2	9	11
Yes	13	21	34
Age			
Median (range)	55.1 (35.9 – 67.7)	50.7 (21.0 – 69.9)	51.3 (21.0 – 69.9)
Time since diagnosis			
Median (range)	430 (9.0 – 5694.0)	476 (28.0 – 1933.0)	430 (9.0 – 5694.0)
Haemoglobin			
Median (range)	7.8 (5.7 – 10.4)	8.0 (5.7 – 9.8)	7.9 (5.7 – 10.4)
White Blood cell Counts			
Median (range)	7.4 (4.5 – 11.3)	6.1 (4.0 – 17.1)	6.4 (4.0 – 17.1)
Creatinine clearance			
Median (range)	79.3 (26.4 – 140.8)	82.2 (41.2 – 146.7)	81.7 (26.4 – 146.7)

Smoking and imatinib pharmacokinetics

The imatinib exposure in smokers versus non smokers was not significantly different; the mean ± SD dose-standardized AUC was 133.6 ± 71.0 ng·h/mL·mg in smokers versus 142.3 ± 84.0 ng·h/mL·mg in non-smokers ($P = 0.78$); the mean Cl/F was 9.6 ± 5.5 L/hr in smokers versus 9.2 ± 4.6 L/hr in non-smokers ($P = 0.84$); the volume of distribution (V_d) was 216.5 ± 114.3 L in smokers versus 207.0 ± 116.9 L in non-smokers ($P = 0.84$) and the half life ($t_{1/2}$) was 16.1 ± 6 h in smokers versus 16.5 ± 6 h in non-smokers ($P = 0.87$; Table 3).

Table 2 Distribution of smokers and non-smokers in the different treatment groups

	Smokers	Non-smokers
400 mg od	1	6
	6.7%	20%
300 mg bid	3	4
	20%	13.3%
400 mg bid	7	18
	47.7%	60%
500 mg bid	4	2
	26.7%	6.7%
Total	15	30

Smoking and imatinib toxicity

The maximum grade of the principal toxicities observed in the study has been tabulated for non-smokers and smokers (Table 4). Grade 2/3 fatigue and anemia were more frequently observed in smokers ($P = 0.0493$ and $P = 0.0258$, respectively). The probability of grade 2/3 fatigue and anemia remained higher in smokers after adjustment for the imatinib dose (logistic model adjusted by dose, P=0.011 and 0.010, respectively).

Smoking and time to progression and overall survival

In the entire population ($n = 45$), non-smoking patients showed a favorable but non significant difference in the overall survival analysis ($P = 0.12$) but not in the time to progression ($P = 0.36$). However, in GIST patients, nonsmokers showed a favorable time to progression ($P = 0.052$) and overall survival ($P = 0.037$; Figs. 1 and 2)

Table 4 Effect of smoking on imatinib induced toxicities

Variables		Smokers *(n = 15)*	Non-smokers *(n = 30)*	*P* value
Edema	Grade 0	1	3	0.1106
	Grade 1	5	19	
	Grade 2	9	7	
	Grade 3	0	1	
Fatigue	Grade 0	1	6	0.0493
	Grade 1	2	13	
	Grade 2	11	8	
	Grade 3	1	3	
Dyspnea	Grade 0	9	24	0.2251
	Grade 1	1	0	
	Grade 2	4	5	
	Grade 3	1	1	
Rash	Grade 0	3	3	0.0628
	Grade 1	10	16	
	Grade 2	2	7	
	Grade 3	0	4	
Infection	Grade 0	10	16	0.4071
	Grade 1	2	6	
	Grade 2	3	7	
	Grade 3	0	1	
Leukopenia	Grade 0	5	7	0.4125
	Grade 1	5	9	
	Grade 2	3	9	
	Grade 3	2	5	
Neutropenia	Grade 0	7	9	0.3581
	Grade 1	5	6	
	Grade 2	0	9	
	Grade 3	1	5	
	Grade 4	2	1	
Thrombocytopenia	Grade 0	12	19	0.0346
	Grade 1	1	1	
	Grade 2	0	0	
	Grade 3	1	0	
	Grade4	1	0	
Anemia	Grade 0	1	3	0.0258
	Grade 1	2	15	
	Grade 2	7	6	
	Grade 3	5	4	

Figure 1 Time to progression in smokers versus non-smokers in GIST patients

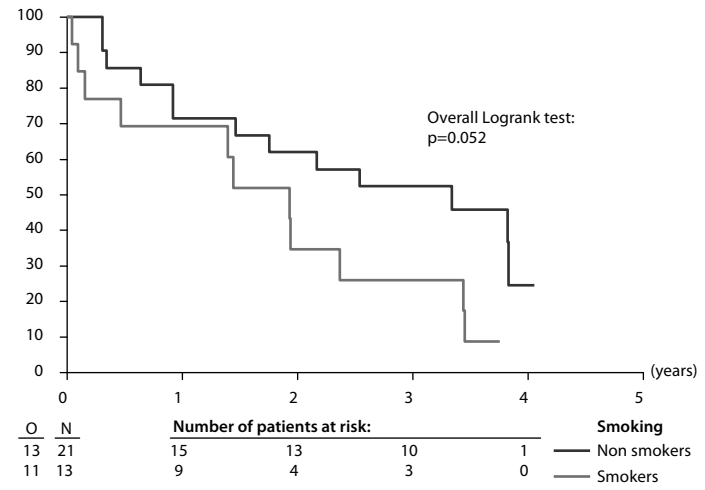
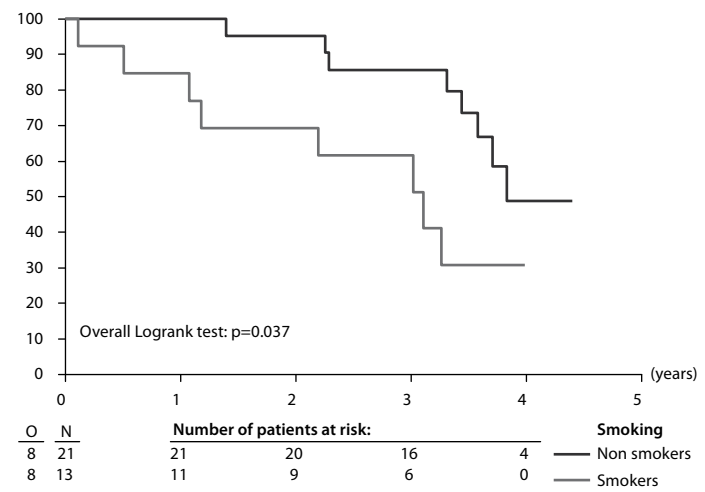


Figure 2 Overall survival in smokers versus non-smokers in GIST patients



Discussion

This study suggests that smoking does not affect the pharmacokinetics of imatinib. However, smoking did increase the risk of some toxicities such as grade ≥ 2 anemia and fatigue. Interestingly, in patients treated with imatinib for GIST, nonsmokers showed a favorable outcome with respect to both time to progression and overall survival.

To date, all interaction studies with imatinib have focused on its primary metabolizing enzyme, CYP3A4 (e.g., the description of the interactions with ketoconazole, rifampicin and St. John's wort)[15-17]. There is one study describing the relationship between genotypes encoding for CYP450 enzymes and ATP-binding cassette transporters thought to play a role in imatinib metabolism and transport, indicating that they do not appear to influence the pharmacokinetics of imatinib significantly in humans. However, the study did show that the Cl/F of orally administered imatinib was slightly reduced in carriers of at least one CYP2D6*4 allele compared with individuals carrying two wild-type CYP2D6 alleles [18]. This might indicate that CYP2D6 plays a more important role in imatinib metabolism *in vivo* than that observed *in vitro*. Imatinib can inhibit certain CYP450 enzymes; hence, although a substrate for CYP3A4 and CYP3A5, it may also inhibit their action, directing metabolism towards other enzymes for which it is a less preferred substrate, such as CYP2D6 and CYP1A2. This emphasizes the importance of exploring the influence of enzymes *in vivo* that appear to only play a minor role in *in vitro* experiments.

In the current retrospective study, smoking habits were retrieved from the medical record and were originally recorded following direct questions about smoking habits before entering the study. We could not validate the smoking status of the patients by measuring the plasma cotinine levels because the plasma samples were not available anymore in this retrospective study. Because ~10% of the patients report not to smoke while smoking, there is a chance of potentially misclassified patients[19]. However this would dilute the outcome of our study because their toxicity profile would be less favorable than the correctly classified patients and they also would negatively influence the time to progression and overall survival. Therefore, 10% misclassification would not influence the conclusion of our study. The specified smoking attitudes of the patients were not noted (e.g., how many tobacco-containing units were consumed what type of tobacco product was used). Therefore, we defined smoking regardless of the quantity of cigarettes smoked per day. We excluded all patients from the analysis for whom the smoking status was not clearly noted, either positively or negatively, in the patients' medical records.

This study is marginally powered (69%) to detect a 50% elevation of the Cl/F of imatinib. Obviously, it could be suggested that a 50% decrease in exposure to a drug is a large effect. However, there are several interactions with cigarette smoking described, which resulted in a >50% decline in exposure (e.g., smoking interactions with theophylline, caffeine, clozapine, olanzapine, flecainide and propranolol)[2, 4, 20-23]. Because our data do not show any effect of smoking on the pharmacokinetics of imatinib, we decided not to expand the study with additional patients.

The absence of an interaction between cigarette smoke and imatinib will most likely be explained by at best a minor role of CYP1A1 and CYP1A2 in imatinib pharmacokinetics *in vivo*. The pharmacokinetic data analyzed in this study were obtained after the first dose of imatinib. Because imatinib is a potent inhibitor of CYP3A4, one may hypothesize that at steady-state pharmacokinetics, imatinib inhibits its own primary metabolizing CYP3A4 pathway and its metabolism is shunted to CYP1A1 and CYP1A2[24]. We can only conclude from our data that metabolism through CYP1A1 and CYP1A2 is not important immediately after starting imatinib therapy, but we cannot exclude an effect of smoking at steady-state pharmacokinetics. Also, other factors that are known to influence the apparent clearance of imatinib should be considered (α1-acid glycoprotein , albumin, body weight, hemoglobin and WBC counts)[25-27]. Elevated α1-acid glycoprotein levels are often seen in cancer patients and with increasing age[12, 28]. However, smoking does not significantly influence the α1-acid glycoprotein levels[29]. In our study, age, body weight, albumin, hemoglobin and WBC counts seems to be equally distributed between the two groups. α1-Acid glycoprotein was not measured, but we have no reason to believe that these factors are unequally distributed between the smoking and non-smoking groups. We studied the most prevalent imatinib toxicities: edema, fatigue, nausea, skin rash, anemia, infection, leucopenia, neutropenia and thrombocytopenia. Except for neutropenia, all toxicities have been shown to be highly dose dependent[30]. In our study, smokers received a higher mean dose of imatinib compared with nonsmokers, which could explain the higher incidence of toxicities in the former group. However, on adjustment for the imatinib dose using multivariate analysis, the increased risk of toxicity in smokers remained significant. Therefore, it is more plausible that the relation of smoking with toxicity is causal[31].

Interestingly, in patients treated for GIST with imatinib, smokers had a significant shorter time to progression and overall survival, which is obviously not explained by differences in imatinib exposure. A possible explanation may be that smokers harbor unfavorable somatic mutations that make the tumor less sensitive to the tyrosine kinase inhibitor and hence are related to a worse outcome. However, in 19 nonsmokers and 11 smokers, we detected a limited set of somatic mutations in *cKIT* exons 11, 9, 13 and *PDGFRA* exon 18 in the GIST tumors and found no differences between smokers and non-smokers (data not shown). In this study, we explored multiple outcomes that might introduce the risk for chance findings. The outcomes of this study are highly correlated (e.g., anemia and fatigue and time to progression and overall survival); however, they should be interpreted as hypothesis-generating and need confirmation.

Currently, little is known of the effect of smoking on the metabolism of most anticancer

drugs. Since imatinib is a substrate for CYP1A2 and CYP1A1 *in vitro*[7,8], it was anticipated that smoking might have an effect on imatinib exposure comparable to erlotinib[6]. Recently, a significant effect of smoking was observed in irinotecan exposure, a chemotherapeutic drug not primarily metabolized by CYP1A1 and CYP1A2[32]. This result emphasizes the importance of studying the effect of smoking on the pharmacokinetics of anticancer drugs, including those for which clearance by CYP1A1 and CYP1A2 is a minor metabolic route, given that ~ 30% of both female and male cancer patients smoke[33].

In conclusion, this exploratory study suggests that smoking is not associated with altered pharmacokinetics of imatinib and more specifically with reduced systemic drug exposure. However, it does show that smokers have an increased risk for grade ≥ 2 anemia and fatigue. GIST patients who smoke may experience a shorter overall survival and a shorter time to progression on treatment with imatinib, but this observation is hypothesis generating and warrants further exploration.

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