PHASE I STUDIES

Pharmacogenetics of telatinib, a VEGFR-2 and VEGFR-3 tyrosine kinase inhibitor, used in patients with solid tumors

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Summary *Purpose* Telatinib is an orally active small-molecule tyrosine kinase inhibitor of kinase insert domain receptor (*KDR; VEGFR-2*) and fms-related tyrosine kinase 4 (*FLT4; VEGFR-3*). This study aims at the identification of relationships between single nucleotide polymorphisms (SNPs) in genes encoding for transporter proteins and pharmacokinetic parameters in order to clarify the significant interpatient variability in drug exposure. In addition, the potential relationship between target receptor polymorphisms and toxicity of telatinib is explored. *Methods* Blood samples from 33 patients enrolled in a phase I dose-escalation study of telatinib were analyzed. For correlation with dose normalized $AUC_{(0–12)}$, ATP-binding cassette (ABC) B1 (*ABCB1*), *ABCC1*, and *ABCG2* were the genes selected. For correlation with telatinib toxicity, selected genes were the drug target genes *KDR* and *FLT4*. *Results* No association between dose normalized $AUC_{(0–12)}$ and drug transporter protein polymorphisms was observed. In addition, no association between toxicity and *KDR* or *FLT4* genotype or haplotype was seen. *Conclusions* Our pharmacogenetic analysis could not reveal a correlation between relevant gene polymorphisms and clinical and pharmacokinetic observations of telatinib.

Keywords Pharmacogenetics · VEGFR · Telatinib · Cancer · Angiogenesis

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Introduction

Single nucleotide polymorphisms (SNPs) in genes encoding for drug transporters and drug targets contribute to interindividual heterogeneity of drug efficacy and toxicity in cancer therapy [1, 2]. This type of research is referred to as pharmacogenetics. In our current study we analyze pharmacogenetic factors likely to be involved in telatinib disposition and mechanism of action.

Telatinib (BAY 57-9352) is an orally active, small-molecule tyrosine kinase inhibitor of kinase insert domain receptor (*KDR;* vascular endothelial growth factor receptor *(VEGFR)-2*) and fms-related tyrosine kinase 4 (*FLT4; VEGFR-3*). Telatinib is metabolized by various cytochrome P450 (CYP) isoforms including *CYP3A4/3A5, CYP2C8, CYP2C9,* and *CYP2C19* as well as by uridine diphosphate glucuronosyltransferase 1A4 (*UGT1A4*), with the formation of the N-glucuronides of telatinib as the major biotransfor-

mation pathway in man. In vitro studies showed telatinib to be a weak substrate of the adenosine triphosphate binding cassette (ABC) B1 (*ABCB1*) transporter (data on file at Bayer Pharmaceuticals Corporation) [3].

In a phase I and pharmacological study we showed that pharmacokinetics (PK) of telatinib were dose proportional [4]. However, substantial interpatient variability was observed (C_{max} and $AUC_{(0–12)}$ % coefficient of variation 20–150%) and no clear association between telatinib exposure and toxicity could be established. However, in this class of agents an increase in toxicity is generally observed with increasing dose [5, 6]. Although in general limited information on drug metabolism and toxicity is available in early stages of drug development, pharmacogenetic research may be valuable. For example, if significant side effects could be linked to a certain drug transporter polymorphism, this could influence further drug development or could become an important issue in patient selection.

The current study examines the potential relationships between SNPs in genes coding for transporter proteins and pharmacokinetic parameters of telatinib in order to identify factors contributing to the significant interpatient variability in drug exposure. In addition, this study explores the potential relationship between target receptor polymorphisms and toxicity of telatinib.
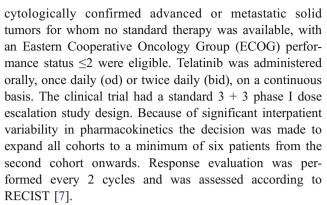
Methods

This study was conducted in a subset of patients enrolled into a two-centre, phase I dose-escalating study of telatinib [4]. The aim of this exploratory pharmacogenetic study was to identify possible relationships between SNPs in genes coding for drug transporters and PK parameters; and drug target related SNPs and side effects of telatinib. From 33 of the 53 patients treated in the phase I study residual blood samples were available for pharmacogenetic analyses. Demographic, toxicity and pharmacokinetic characteristics were comparable for included and excluded patients (data not shown). Four of these 33 patients were treated with telatinib oral solution or 25 mg tablets, the remaining patients with 150 mg tablets.

Since bioavailability of the telatinib formulations differ, a decision was made to restrict the current analysis to one telatinib formulation. Therefore, in the association analysis with PK, only the 29 patients treated with the 150 mg tablets were included.

Patients and samples

Eligibility criteria, drug administration procedures and clinical and pharmacokinetic results are described in detail elsewhere [4]. Briefly, patients with histologically or cytologically confirmed advanced or metastatic solid tumors for whom no standard therapy was available, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 were eligible. Telatinib was administered orally, once daily (od) or twice daily (bid), on a continuous basis. The clinical trial had a standard 3 + 3 phase I dose escalation study design. Because of significant interpatient variability in pharmacokinetics the decision was made to expand all cohorts to a minimum of six patients from the second cohort onwards. Response evaluation was performed every 2 cycles and was assessed according to RECIST [7].

Residual blood samples taken for the routine patient care were stored at −20°C at the local hospital laboratories. One frozen blood sample for each patient was collected from the two participating hospitals (Leiden University Medical Center, Leiden and Erasmus Medical Center, Rotterdam). All samples were anonymized by a third party, according to the instructions given in the "Code of Conduct for the use of data in Health Research" and "Code for Proper Secondary Use of Human Tissue" (www.federa.org). Approval from the institutional medical ethical review boards was obtained.

Pharmacokinetic and toxicity parameters

PK evaluation was performed by collecting blood samples on days 1 and 14 of cycle 1, and day 14 of cycles 2 and 4. Pharmacokinetic parameters were calculated by non-compartmental analysis using WinNonlin (version 4.1.a).

In this study cycle 1 day 14 (representing steady-state) dose normalized $AUC_{(0–12)}$, calculated as $AUC_{(0–12)}$/actual dose administered, was selected as the most important PK parameter to associate with transporter genetic polymorphisms. Dose normalized C_{max}, T_{max} and $T_{1/2}$ were also selected for association analyses.

Patients were evaluated for adverse events and toxicity according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0. In general, the NCI-CTC toxicity score distinguishes between mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling toxicity (grade 4) and death related to adverse events (grade 5). Telatinib administration resulted in limited toxicity. Grade 3–4 toxicity was only seen in 3 patients. Therefore, despite the fact that grade 3–4 toxicity is more clinically relevant, the occurrence of any grade 1–4 toxicity was considered to be the best candidate parameter for association analyses with drug target receptor genetic polymorphisms. Since toxicity observed in the first cycle was limited we decided to use overall toxicity observed in all treatment cycles for statistical association studies. In addition, hypertension is considered to be one of the more serious telatinib side

effects, and grade 1–4 hypertension was also selected for association analyses.

Selection of candidate genes

Candidate genes were selected based on the information of preclinical pharmacology studies as reported in the Investigator's brochure (Bayer Pharmaceutical Corporation, data on file). For association with PK parameters *ABCB1*, *ABCC1*, and *ABCG2* were the genes selected. For correlation with telatinib toxicity selected genes were the drug target genes encoding *KDR* and *FLT4*. For the major biotransformation pathway in man, the formation of the N-glucuronides through *UGT1A4*, no SNP met the criteria for selection described below.

The SNPs were selected, taking into consideration one or more of the following criteria: validated SNP assay, SNP causes preferably non-synonymous amino acid change, indications for clinical relevance from previous publications, and a preferred minor genotype frequency of ~10%.

DNA extraction and SNP analysis methods

DNA was isolated from whole blood samples with MagNA Pure DNA Isolation kit (Roche Diagnostics, Almere, The Netherlands). DNA concentrations were quantified using a NanoDrop spectrophotometer (Isogen, IJsselstein, The Netherlands). Taqman assays were obtained from Applied Biosystems (Applied Biosystems, Nieuwerkerk aan den IJssel, The Netherlands). As a quality control, 4 samples were genotyped in duplicate for all assays and 2 assays were tested in duplicate on all samples. As negative controls water was used. Overall, no inconsistencies were observed in the results.

The following SNPs were analyzed: *ABCB1* 3435C>T (rs1045642), *ABCB1* 1236C>T (rs1128503), *ABCB1* 2677G>A/T (rs2032582), *ABCB1* -129T>C, *ABCC1* C>G (rs129081), *ABCC1* 825T>C (rs246221), *ABCC1* 1062T>C (rs35587), *ABCC1* 2012G>T (rs45511401), *ABCG2* 346G>A (rs2231137), *ABCG2* 421C>A (rs2231142), *FLT4* 1480A>G (rs307826), *FLT4* 2670C>G (rs448012), *KDR* 1719A>T (rs1870377), *KDR* -604T>C (rs2071559), and *KDR* 1192G>A (rs2305948).

SNP genotyping was performed with BIOMARK 48.48 dynamic array (Fluidigm Corporation, South San Francisco, CA, USA). All assays were performed according to protocols provided by the manufacturer.

Statistical analysis

Differences in pharmacokinetic and toxicity parameters among genotypes were analyzed by Student's *t*-test, ANOVA or Kruskal–Wallis test for continuous variables or chi-square test for dichotomous variables where appropriate. For

toxicity, differences in genotype distribution were tested by 3×2 cross-tabulations for each genotype, and by 2×2 cross-tabulations for carriers versus noncarriers, with analysis by 2-sided chi-square test.

Polymorphisms within a gene were tested with the chi-square test (P-value<0.05) to detect linkage disequilibrium (LD). If LD between SNPs was detected, haplotypes were determined for each individual with gPLINK (http://pngu.mgh.harvard.edu/purcell/plink/) [8]. No phase uncertainty in the defined haploblocks and haplotypes (Rh^2> 0.98) was seen.

Associations between the number of copies of a haplotype and clinical parameters were performed using a chi-square test for dichotomous variables and Student's *t*-test, ANOVA or Kruskal–Wallis test for continuous variables.

Table 1 Patient characteristics, overall telatinib-induced toxicity, pharmacokinetic results and outcome data of telatinib treated patients

Characteristics	Patients (n (%))
Gender	
Male	15 (45)
Female	18 (55)
Age, years	
Mean (range)	53 (22–77)
Tumor type	
Soft tissue sarcoma	9 (27)
Colorectal cancer	5 (15)
Adrenal cancer	3 (9)
Ovarian cancer	3 (9)
Cholangiocarcinoma	2 (6)
Esophageal cancer	2 (6)
Melanoma	2 (6)
Miscellaneous	7 (21)
ECOG performance score	
0	9 (27)
1	24 (73)
Nr of previous treatment lines	
Mean (range)	3 (0–13)
Toxicity	
Any toxicity grade 1–4	23 (70)
Any toxicity grade 3 or 4	3 (9)
Hypertension grade 1–4	7 (21)
Hypertension grade 3 or 4	2 (6)
Pharmacokinetic parameters	
Mean (range)	
Dose normalized $AUC_{(0-12)}$ (μg.hr/L per mg of dose)	9.26 (0.98–34.60)
Number of treatment courses	
Mean (range)	5.5 (1–30)

ECOG Eastern Cooperative Oncology Group, Dose normalized AUC: area under the curve/dose

All statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL) and were two-sided, with a level of significance of $\alpha=0.05$.

Results

Baseline patient characteristics, observed treatment-related toxicities, pharmacokinetics and treatment duration are presented in Table 1. Telatinib doses used were 20 mg od ($n=2$), 75 mg od ($n=2$), 150 mg bid ($n=4$), 300 mg bid ($n=4$), 600 mg bid ($n=3$), 900 mg bid ($n=16$), and 1,500 mg bid ($n=2$). Our population comprised 100% Caucasians with 45% males and 55% females. Most frequent tumor types were soft tissue sarcomas (27%) next to colorectal cancer (15%) together with a high number of other tumor types (58%) consistent with the phase I nature of the clinical study. Median number of treatment courses was 5.5, ranging from 1 to 30, with one course being 3 weeks of telatinib administration.

Table 2 Association between genetic polymorphisms and telatinib pharmacokinetic data. Dose normalized AUC

Gene	Polymorphism	Genotype	No.	Dose normalized AUC Mean	SD
ABCB1	3435C>T	CC	7	7.30	3.35
		CT	16	11.10	9.10
		TT	6	6.65	4.76
		P-value		0.343	
	1236C>T	CC	9	7.84	3.26
		CT	15	11.60	9.44
		TT	5	4.82	1.81
		P-value		0.180	
	2677G>A/T	GG	9	7.84	3.26
		TG	15	11.60	9.44
		TT	5	4.82	1.81
		P-value		0.180	
	-129T>C	TT	26	8.67	7.51
		TC	2	15.65	6.06
		CC	1	11.79	n.a.
		P-value		0.134	
ABCC1	#(rs129081)	CC	5	10.22	7.57
		GC	15	10.44	9.07
		GG	9	6.77	3.16
		P-value		0.494	
	825T>C	TT	18	8.26	6.54
		TC	11	10.90	8.76
		P-value		0.362	
	1062T>C	TT	17	8.36	6.73
		TC	10	9.95	9.15
		CC	2	13.45	3.30
		P-value		0.631	
	2012G>T	GG	24	8.80	5.89
		GT	4	13.46	14.57
		TT	1	3.63	n.a.
		P-value		0.552	
ABCG2	346G>A	GG	25	9.78	7.83
		AG	4	6.00	2.69
		P-value		0.353	
	421C>A	CC	23	8.95	7.96
		CA	6	10.48	5.26
		P-value		0.661	

#=*801 number from termination codon TGA (5397). 3UTR

Table 3 Association between genetic polymorphisms and telatinib pharmacokinetic data. Dose normalized C_{max}, $T_{1/2}$ and T_{max}

Gene	Polymorphism	P-value		
		Dose normalized Cmax	T1/2	Tmax
ABCB1	3435C>T	0.474	0.069	0.274
	1236C>T	0.220	0.586	0.597
	2677G>A/T	0.220	0.586	0.597
	−129T>C	0.140	0.236	0.350
ABCC1	#(rs129081)	0.962	0.393	0.618
	825T>C	0.152	0.465	0.582
	1062T>C	0.180	0.661	0.705
	2012G>T	0.313	0.891	0.721
ABCG2	346G>A	0.253	0.705	0.627
	421C>A	0.498	0.399	0.280

#=*801 number from termination codon TGA (5397). 3UTR

Telatinib toxicity was generally mild, with any grade 1–4 toxicity during all treatment cycles occurring in 23 out of 33 patients (70%). Grade 3–4 toxicity was only observed in 3 patients. Hypertension was the most frequently observed side-effect (n=7) and was unrelated to dose [9].

The success rates for all genotyping assays were 100%. Genotype frequencies for 13 of 15 SNPs were in Hardy-Weinberg equilibrium ($P>0.05$). ABCB1 -129T>C and ABCC1 2012G>T did not adhere Hardy-Weinberg equilibrium, which was most likely caused by the limited population size. Genotype frequencies for both SNPs were in line with previous publications and frequencies reported in the NCBI database (www.ncbi.nlm.nih.gov).

There was no association between telatinib dose normalized AUC$_{(0–12)}$ and genetic polymorphisms in ABCB1,

ABCC1, or ABCG2 (Tables 2 and 3). Haploblock for ABCB1 included 3435C>T, 1236C>T, and 2677G>A/T; haploblock for ABCC1 included 825T>C, and 1062T>C. Haplotype frequencies for ABCB1 were TTT 0.392, CTT 0.017, TCG 0.093, and CCG 0.498, and for ABCC1 CC 0.197, TC 0.061, and TT 0.724. Also ABCB1 and ABCC1 haplotypes did not show an association with telatinib dose normalized AUC$_{(0–12)}$. There was also no association between genetic polymorphisms in ABCB1, ABCC1, or ABCG2 and other investigated PK parameters, i.e. dose normalized C_{max}, T_{max} and $T_{1/2}$ (Tables 2 and 3).

The number of telatinib treatment courses was not related to any of the genetic polymorphisms and haplotypes analyzed. Since this was an exploratory study with a relatively small number of patients, different dose levels,

Table 4 Association between genetic polymorphisms and telatinib-induced toxicity

Gene	Polymorphism	Genotype	Toxicity: any toxicity grade 1–4 all cycles		P-value
			No	Yes	
FLT4	1480A>G	AA	7	20	0.336
		AG	3	3	
	2670C>G	CC	6	11	0.813
		CG	3	9	
		GG	1	3	
KDR	1719A>T	AA	1	1	0.809
		TA	4	9	
		TT	5	13	
	-604T>C	CC	3	7	0.870
		CT	5	13	
		TT	2	3	
	1192G>A	CC	5	19	0.091
		TC	4	4	
		TT	1	0	

different tumor types, and variable previous treatment lines association analyses between polymorphisms and treatment outcome were not performed.

No association between any grade 1–4 toxicity and *KDR* or *FLT4* genotype or haplotype was observed (Table 4).

Discussion

The development of tailor-made pharmaceutics is especially useful in the field of oncology, as most standard anticancer agents have a very narrow therapeutic index, leading to nonspecific anti-tumor response in combination with a high level of side effects. For example, in 3–5% of patients with severe 5-FU-related toxicity. dihydropyrimidine dehydrogenase (DPD) deficiencies are described [10, 11]. In addition, the genetic variant of the gene encoding UDP glucuronosyltransferase (UGT) 1A1 polymorphism, *UGT1A1*28*, is associated with a higher incidence of toxicity, mostly hematological toxicity, in irinotecan treatment [12–14].

Most research to improve cancer treatment through genetics has focused on polymorphisms in genes encoding the drug transporters and drug metabolizing enzymes but less is known about genetic variation in drug targets. Directing treatment on the vascular endothelial growth factor (VEGF) pathway, one of the key players in angiogenesis, is a focus of more recent research. VEGF inhibitors have only become available for clinical use in the last few years and consequently, very little is known regarding the influence of polymorphisms in VEGF or its receptor, VEGFR [15, 16]. One CA repeat polymorphism in the *KDR* (*VEGFR2)*) gene is described previously, with a higher promoter activity in the 11-repeat polymorphism compared to the 12-repeat polymorphism [17]. Four SNPs in the *KDR* gene were identified by Park et al (-92G>A, 54A>G, 889G>A, and 1416T>A) and associated with atopy [18]. Recently, Schneider et al reported that *KDR* genotypes were not associated with toxicity or efficacy of paclitaxel with or without bevacizumab treatment in advanced breast cancer patients [19].

VEGF inhibitors can induce very specific side effects which are hard to predict. This is even more relevant while in future use these angiogenesis inhibitors most likely will be combined with various chemotherapeutic agents. Pharmacogenetic research might help to identify the patients at risk for specific side effects and select patients or doses needed for optimal treatment without adding potentially harmful side effects.

In this exploratory study we could not find an association between polymorphisms in genes encoding transporter proteins and telatinib pharmacokinetics or between drug target gene polymorphisms and telatinib induced toxicity. This lack of association might be explained by, for example,

the limited number of patients, the relatively limited toxicity, and the variability in tumor types, number of previous treatment lines, and performance scores. Since toxicity was limited we used toxicity reported over all treatment cycles. This may have caused bias, and therefore number of treatment cycles was used as a covariate in the multivariate analysis. Since different telatinib doses were used, we corrected by associating polymorphisms with dose normalized $AUC_{(0–12)}$.

Pharmacogenetic testing is important for all new drug applications. Knowledge on pharmacokinetics and pharmacodynamics of both registered and new developing drugs is increasing far more rapidly than the knowledge on genetic variants in metabolizing enzymes, transporters and drug target genes [1, 20, 21]. Therefore, DNA collection for future genetic studies, retrospective and prospective, is required and all patients in clinical trials should be asked to consent for DNA collection for future studies. Often side effects are based on single gene polymorphisms affecting drug metabolism, interaction with cellular targets or transport. Therefore, hypothesis based pharmacogenetic research of candidate genes is important in phase I and II studies to limit the number of patients unnecessarily exposed to a toxic dose or drug. This information may reduce the size, costs and duration of subsequent phase III studies.

In general, in the preclinical and phase I setting little is known about drug pharmacokinetics and pharmacodynamics. With this exploratory study we tried to increase that knowledge, because, despite of the rapidly increasing use of VEGF inhibitors, the knowledge of determinants that predict response and toxicity in the individual patient is still lacking. Therefore, it remains highly important to conduct pharmacogenetic association studies in early drug development in order to increase knowledge on interpatient variability of drug response.

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