Review Article

Role of pharmacogenetics in personalised imatinib dosing

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Abstract: Imatinib is the original tyrosine kinase inhibitor specifically designed and clinically used for the molecularly targeted treatment of chronic myeloid leukaemia (CML). It remains one of the most widely used first-line treatments for CML, and is now also indicated in multiple other BCR-ABL-, c-KIT- and PDGFR-driven cancers. Imatinib is orally administered, predominantly hepatically cleared with a low hepatic extraction ratio, is 95% bound to plasma proteins, and has an intracellular site of action. In the CML setting, treatment outcomes correlate with plasma imatinib concentrations, which show large interpatient variability. Treatment outcomes also correlate with markers of drug transporter variability considered to influence imatinib distribution into CML cells. Personalised imatinib dosing is therefore expected to improve treatment outcomes compared to a "one-dose-fits-all" approach, with a potential additional role for pharmacogenetics. Imatinib is metabolised by CYPs 2C8 and 3A4 *in vitro*. *CYP2C8* genotype significantly affects imatinib metabolism, and consequently imatinib systemic exposure in CML patients. Conversely, there is no consistent evidence that CYP3A4 or CYP3A5 inhibitors, inducers or genetics alter imatinib metabolism and pharmacokinetics clinically. Imatinib is also a substrate for uptake and efflux transporters expressed in the liver and/or CML cells, although exactly which transporters is an area of open debate. The clear majority of studies indicate no significant effect of transporter genotypes on plasma imatinib concentrations or clearance, and any positive findings to date have not been replicated. Various measures of CML treatment outcome have been correlated with transporter genotype, and from this implied an effect of transporter genetics on imatinib distribution into CML cells. However, due to study design limitations it is unclear if these observations are due to genetic effects on imatinib clearance, intracellular distribution, or possibly neither. Other potentially novel genetic factors influencing imatinib disposition, such as xenobiotic-responsive receptor gene polymorphisms, remain to be thoroughly investigated. In summary, studies to date indicate a potential genetic influence on imatinib disposition, however evidence is still lacking to support a pharmacogenomic approach to personalised imatinib dosing. Whether pharmacogenomic information might be complementary to potential therapeutic drug monitoring or target concentration intervention for imatinib is an ongoing question. Improved study designs are required to gain greater mechanistic understanding of the factors governing variable imatinib intracellular distribution and its relationship to response, and move toward improved tools for personalised imatinib dosing.

Keywords: Imatinib mesylate; chronic myeloid leukaemia; pharmacogenetics

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Introduction

Imatinib was the first of the tyrosine kinase inhibitor class of molecularly targeted cancer treatments. It was specifically designed to target the BCR-ABL tyrosine kinase responsible for chronic myeloid leukaemia (CML) pathogenesis, and remains one of the most widely used first-line treatments for CML. Imatinib is also indicated for BCR-ABL-positive acute lymphoblastic leukaemia and, because it also inhibits the c-KIT and PDGFR tyrosine kinases, for c-KIT- and PDGFR-positive gastrointestinal stromal tumours (GISTs), myelodysplastic/myeloproliferative diseases associated with *PDGFR* gene re-arrangements, aggressive systemic mastocytosis (without D816V c-Kit mutation), hypereosinophilic syndrome and/or chronic eosinophilic leukaemia, and dermatofibrosarcoma protuberans (1-4).

As the indication with the longest history and greatest body of research, and clearest need for personalised dosing, this review will focus on the role of pharmacogenetics in personalised imatinib dosing in the context of CML. However, findings from GIST patients will also be discussed that aid our understanding of genetic contributions to imatinib pharmacokinetics. Furthermore, the conclusions drawn from our experience with imatinib in CML patients should also help inform future imatinib pharmacogenetics research in these other indications.

Then need for personalised imatinib dosing

The arrival of imatinib in 2001 revolutionised CML treatment and dramatically improved patient prognosis compared to the pre-imatinib era. Imatinib dose recommendations for CML treatment have since remained essentially unchanged; a starting dose of 400 mg once daily for all patients, with treatment generally expected to be non-curative and requiring indefinite chronic dosing. However, up to 50% of CML patients will discontinue imatinib due to lack of efficacy or adverse effects when using this one-dose-fits-all approach (5); a significant problem requiring switching to other treatments which may be more costly or may have significant toxicities.

The importance of early treatment response

CML treatment efficacy is defined mainly by reduction of BCR-ABL-positive metaphases in bone marrow (cytogenetic response) and reduced *BCR-ABL* expression in blood cells (molecular response). Standard guidelines identify optimal and suboptimal response, and treatment failure, based on milestones of cytogenetic and molecular response over the course of treatment (6). Suboptimal treatment response can be broadly categorised into two forms; primary resistance and secondary resistance (7), outlined in *Table 1*.

Both forms of resistance can be major hurdles for the long-term survival of patients. However, the importance of early treatment response has been increasingly recognised, and typically sets the scene for longer-term outcomes. For example, early molecular response [(EMR) ≤10% *BCR-ABL* transcript at 3 months] is prognostic of long-term responses, including progression-free and overall survival (8). Unfortunately, one in four patients fail to achieve EMR, and will have poorer long-term prognosis regardless of whether their imatinib dose is increased or are switched to other tyrosine kinase inhibitors (8). Therefore, it is important to optimise treatment early to avoid primary resistance.

Determinants of variable imatinib response

Interpatient variability in imatinib disposition is a major determinant of variable imatinib response, particularly primary resistance. Steady-state trough total plasma imatinib concentrations (C_{ss}) can vary more than 25-fold in CML patients administered the same dose (9,10), and are correlated with both CML and GIST treatment responses (5,11). As imatinib has an intracellular site of action, variability in its distribution into CML cells is also a likely, though far less well characterised, contributor to variable response. Therefore, understanding key contributors to interpatient variability in imatinib disposition is essential for the optimisation of its treatment through dose individualisation.

Pharmacodynamic factors, such as acquired kinase domain mutations, play an important role in secondary resistance (7). However, since secondary resistance is unlikely to be overcome by imatinib dose adjustment, and typically necessitates switching to second-line TKIs, these factors are not covered further in this review.

Imatinib pharmacokinetics

Imatinib has high oral bioavailability (95–100%), with peak plasma concentrations approximately 2 hours after administration (12,13). It is highly (~95%) bound to plasma proteins, with volume of distribution estimates ranging from ~170–430 L (13). Imatinib total clearance is

Table 1 General categorisation and likely mechanisms of imatinib treatment resistance

Category	Definition	Treatment stage	Likely mechanisms
Primary resistance	Failure to reach treatment milestone(s)	Early: typically within first 6–18 months	Intrinsic resistance, e.g., patient &/or CML cell phenotypes affecting imatinib disposition
Secondary resistance	Loss of a previously achieved treatment response	Later (typically)	Acquired resistance, e.g., kinase domain mutations; upregulated imatinib efflux, or downregulated imatinib influx, transporters

CML, chronic myeloid leukaemia.

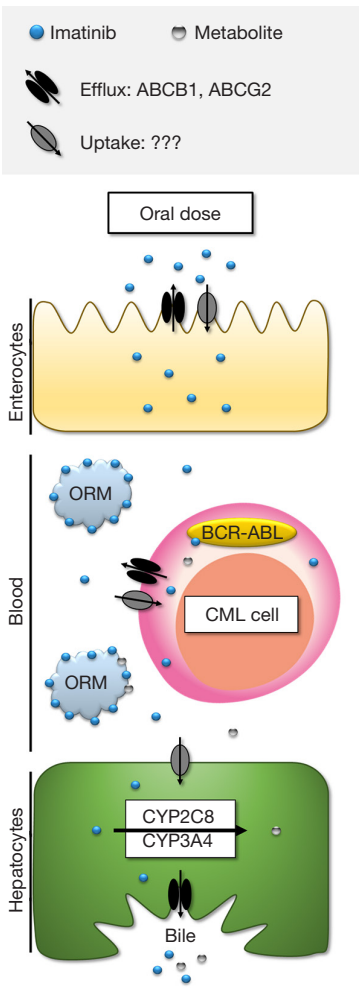

Figure 1 Key contributors to imatinib disposition in chronic myeloid leukaemia patients. ORM, orosomucoid/alpha-1-acid glycoprotein (AAG); CML, chronic myeloid leukaemia.

approximately 9–14 L/h, with a half-life of 12–34 hours, and it is predominantly hepatically (<15% renal) cleared (13,14). With an intrinsic hepatic clearance of approximately 15 L/h (15), imatinib is a low hepatic extraction drug, and therefore steady-state total plasma imatinib concentrations are determined by variability in plasma protein binding and intrinsic hepatic clearance (metabolism and transport).

Importantly, imatinib has an intracellular site of action, and so variability in imatinib distribution into target CML cells is also likely to be relevant for imatinib efficacy. However, at present no *in vivo* CML cell intracellular concentration-response relationship has been tested or shown empirically.

The key contributors to imatinib disposition are thus summarised in *Figure 1*, and discussed in more detail in the following sections.

Plasma protein binding

Imatinib is highly (~95%) bound to plasma proteins, primarily alpha-1-acid glycoprotein (AAG) (13). Plasma AAG concentrations vary substantially (over 5-fold) between CML patients (16), and will determine the unbound fraction of imatinib available for total clearance and distribution into CML cells. Consequently, variable plasma AAG concentrations contribute significantly to inter-individual variability in total imatinib clearance (~10–20% of co-efficient of variation) (17,18), as well as confounding the total plasma imatinib concentration-response relationship.

Metabolism

Imatinib undergoes hepatic N-demethylation to the much less potent (3- to >10-fold higher IC_{50}) (19-22) major metabolite N-desmethyl imatinib (NDIM); steady-state total plasma NDIM concentrations are approximately 20% that of imatinib (10,23,24). Both imatinib and NDIM undergo mostly hepatic excretion with very little renal contribution (13). Therefore, imatinib biotransformation to NDIM is a clinically important inactivating process, with variable imatinib metabolism likely to be a major contributor to the large inter-patient variability in plasma concentrations (25,26).

In vitro studies using recombinant enzymes indicate that imatinib is N-demethylated by both CYP3A4 and CYP2C8, and possibly CYP3A5, whilst other enzymes (CYP1A2, CYP2D6, CYP2C9 and CYP2C19) play little or no role (27-30). CYP3A4 inhibition studies employing single imatinib doses in healthy participants also indicate a role for CYP3A4 in imatinib *in vivo* metabolism (31,32). Based on these studies, and the relative abundance of hepatic CYP3A4 compared to CYP2C8, it has long been accepted that CYP3A4 is the major or even sole enzyme responsible for imatinib metabolism in CML patients.

However, steady-state imatinib pharmacokinetics are not significantly influenced by CYP3A4 inducers or inhibitors (13,33,34), and are unrelated to variability in markers of CYP3A activity in CML (35) or GIST patients (36,37). We have also recently demonstrated that imatinib N-demethylation in human liver microsomes is mainly mediated by CYP2C8, and not CYP3A4 (38), potentially as a result of imatinib dose- and time-dependent mechanism-based CYP3A4 inhibition identified in other *in vitro* studies (29). Consequently, the dominant role of CYP3A4 in imatinib metabolism clinically is coming under question, with CYP2C8 metabolism emerging as a potential major contributor.

Transport

As shown in *Figure 1*, drug transporters that influence imatinib uptake and efflux could theoretically affect imatinib disposition at multiple levels. For example, uptake transporters in enterocytes could facilitate imatinib absorption. Imatinib is a quadrivalent base [acid dissociation constants (pKa) =1.52, 2.56, 3.73 and 8.07], and is predominantly cationic at pH 6 and below (39). Therefore, it is speculated that an active intestinal uptake process is required to explain imatinib's high bioavailability. Efflux transporters could conversely limit imatinib absorption, however high imatinib bioavailability would suggest efflux transporters don't play a significant role in absorption. Drug transporters could also play a role in imatinib uptake and retention in target cancer cells, which has been the focus of extensive *in vitro* research to date with respect to mechanisms of primary and secondary imatinib resistance (40). Imatinib is partially charged (~33% monocationic) with a distribution co-efficient (logD) of 0.8 at pH 7.4 (41). However, imatinib has a high intracellular: plasma concentration ratio (~8) (42) in patients' peripheral blood mononuclear cells, indicating an active uptake mechanism. Finally, both influx and efflux transporters expressed on hepatocytes could act to facilitate imatinib biotransformation and excretion, and thus contribute to imatinib clearance.

Evidence for the impact of drug transporters on TKI disposition was recently extensively reviewed (40), and the expert conclusions of Neul and colleagues regarding imatinib can be summarised as follows:

Efflux: imatinib is a substrate of the ABCB1 (P-glycoprotein) and ABCG2 (Breast Cancer Resistance Protein, BCRP) efflux transporters *in vitro*, and its distribution is significantly altered in Abcb1 and/or Abcg2 knockout mice.

Uptake: whilst SLC22A1 (organic cation transporter, OCT1) has long been touted as a key imatinib transporter, the majority of *in vitro* and *in vivo* evidence now indicates that OCT1 is not a significant contributor to imatinib uptake. Similarly, no other uptake transporters investigated to date (SLCO1A2, SLCO1B1, SLCO1B3, SLC22A2-8, SLC47A1) significantly influence imatinib intracellular accumulation. Thus the major transporter(s) responsible for imatinib uptake remains unknown.

We support Neul and colleagues' recommendations for more appropriate, well-designed, controlled and standardised transporter assays that properly characterise the transport of imatinib. As detailed below, much time and resources may have been misdirected on pharmacogenetic studies of transporters now considered irrelevant to imatinib disposition. No studies have to date investigated the influence of transporter variability (e.g., expression, inhibition, genetics) on imatinib intracellular concentrations in patient cells. This, alongside demonstrating an imatinib intracellular concentration-response relationship clinically, will be critical for translating the extensive *in vitro* and pharmacogenetic research on transporter-mediated mechanisms of imatinib resistance into improvements in patient outcomes.

Pharmacogenetic studies

Patient germline genetics can potentially play a role in primary resistance. Polymorphisms in genes involved in plasma protein binding (*ORM1*), metabolism (CYPs) and transport (e.g., *ABCB1*, *ABCG2*) are hypothesised to influence the relationship between imatinib dose and total plasma imatinib concentrations. Polymorphisms in genes of transporters expressed in CML cells are also hypothesised to influence intracellular distribution, and thus the plasma concentration-response relationship. Each of these key

factors will be discussed in turn.

Plasma protein binding genetics

Plasma AAG comprises a combination of *ORM1* and *ORM2* gene products (orosomucoid-1 and -2, respectively); imatinib binds primarily to orosomucoid-1 (ORM1) (43). Concentrations and ratios of ORM1 and orosomucoid-2 vary between individuals, and are altered significantly by diseases such as cancer (43,44). In addition, there are three *ORM1* haplotypes determined by non-synonymous polymorphisms at two loci (rs17650 113G>A Arg38Gln and rs1126801 Val174Met); **F1* (38Gln-174Val), **F2* (38Gln-174Met) and **S* (38Arg-174Val). The 38Gln allele is common (50–70%) and has been reported to influence the unbound fraction of quinidine (45) and pharmacokinetics of telmisartan (46), whilst the 174Met allele is rare (0–5% globally). Thus, in addition to variability in AAG expression, polymorphisms in the *ORM1* gene could further increase inter-individual variability in imatinib unbound fraction, and thus total imatinib clearance, further confounding the total plasma imatinib concentration-response relationship. To date however, the impact of *ORM1* polymorphisms on imatinib unbound fraction have yet to be characterised *in vitro*. In the only clinical study to date, Petain and colleagues [2008] found no significant difference in population-pharmacokinetic model predictions of imatinib clearance between *ORM1* genotypes among a small sample of 31 paediatric (n=15 *F1/*F1, 1 *F1/*F2, 7 *F1/*S, 7 *S/*S) and 15 adult (n=8 *F1/*F1, 1 *F1/*F2, 3 *F1/*S, 3 *S/*S) GIST patients; imatinib clearance was however significantly negatively correlated with plasma AAG concentrations (17).

Metabolism genetics

Pharmacogenetic studies investigating CYP450 enzyme polymorphisms are summarised in *Table 2*.

CYP3A4/5

Consistent with no impact of CYP3A inhibitors or inducers on imatinib steady-state pharmacokinetics, CYP3A genetics consistently has no significant effect on imatinib pharmacokinetics in CML or GIST patients (*Table 2*). The major polymorphism influencing variability in CYP3A metabolism is *CYP3A5*3* (rs776746, 6986A>G). *CYP3A5*3* homozygotes lack functional CYP3A5, whilst heterozygous and wild-type individuals produce relatively high levels of functional CYP3A5. Despite this, *CYP3A5*3* genotypes have no significant effect on imatinib pharmacokinetics regardless of the population studied (Caucasian or Asian, CML or GIST).

CYP3A4 variability is poorly defined by common genetic polymorphisms, with *CYP3A4* having a relatively low frequency of reduced function allelic variants (53). The two *CYP3A4* polymorphisms (*1B and *18) investigated to date have uncertain functional consequences generally, and had no significant effect on imatinib pharmacokinetics. The more recently identified *CYP3A4*22* polymorphism, associated with decreased CYP3A4 activity and alterations in substrate pharmacokinetics (53), has yet to be investigated with respect to imatinib. However, any potential clinically relevant effect on imatinib pharmacokinetics is dependent on whether CYP3A4 metabolism actually plays a major role in steady-state imatinib clearance.

CYP2C8

*CYP2C8**3 and *4 are the major *CYP2C8* polymorphisms in Caucasians. *CYP2C8**3 is associated with increased or decreased metabolism *in vitro* depending on the substrate, and significant effects on pharmacokinetics (54-62). We initially demonstrated that *CYP2C8*3* is a gain-of-function haplotype for imatinib N-demethylation *in vitro*, and have subsequently shown this to translate into significantly increased imatinib metabolism clinically (10,38).

Conversely, *CYP2C8*4* is typically associated with decreased activity (55,63-65), and we have shown that CML patients carrying the *4 allele have significantly decreased imatinib metabolism (10). *CYP2C8*4* carriers also had 50% higher total plasma imatinib concentrations and were significantly more likely to achieve a study target concentration of 1,000 ng/mL, with all carriers reaching this threshold associated with improved long-term treatment outcomes (10).

Therefore, *CYP2C8* genotyping could foreseeably inform imatinib personalised dosing if these findings are replicated.

Other CYP enzymes

Despite playing little or no role in imatinib metabolism, *CYP2C9*, *CYP2C19* and *CYP2D6* genotype effects on imatinib pharmacokinetics have also been investigated (47-49), but as expected, no significant associations were identified (*Table 2*).

Transporter genetics

More than 30 clinical studies have been published

Table 2 Effect of drug metabolising enzyme genetics on plasma imatinib concentrations and clearance

Gene	SNP/haplotype	Patients	Ethnicity	Study design	N (W/H/V)	PK measure	Result	Reference
CYP2C8	416G>A/1196A>G; *3; R139K/K399R (rs11572080/rs10509681)	CML	Caucasian	Cross-sectional	199 (165/31/3)	NDIM/imatinib metabolic ratio (MR), Css	*3 carriers 27% ↑ MR (P<0.01)	(10)
	792C>G; *4 (rs1058930)	CML	Caucasian	Cross-sectional	199 (184/15/0)	NDIM/imatinib metabolic ratio (MR), Css	*4 carriers 18% ↓ MR (P<0.05), 50% ↑ Css (P<0.05)	(10)
CYP2C9	430C>T; *2; R144C (rs1799853)	GIST	Caucasian	Cross-sectional	70 (60/9/1)	CL/F	NS	(47)
	1075A>C; *3; I359L (rs1057910)	CML	Korean	Cross-sectional	82 (77/5/0)	Css	NS	(48)
		GIST	Caucasian	Cross-sectional	70 (60/10/0)	CL/F	NS	(47)
CYP2C19	681G>A; *2 (rs4244285)	CML	Korean	Cross-sectional	82 (42/37/3)	Css	NS	(48)
		CML	Japanese	Pop-PK	34 (16/13/5)	CL/F	NS	(49)
		GIST	Caucasian	Cross-sectional	70 (40/27/3)	CL/F	NS	(47)
	636G>A; *3; W212Stop (rs4986893)	CML	Korean	Cross-sectional	82 (65/17/0)	Css	NS	(48)
		CML	Japanese	Pop-PK	34 (27/7/0)	CL/F	NS	(49)
CYP2D6	1846G>A; *4 (rs3892097)	GIST	Caucasian	Cross-sectional	70 (42/24/1)	CL/F	NS	(47)
	100C>T; *10B; P34S (rs1065852)	CML	Korean	Cross-sectional	82 (24/35/23)	Css	NS	(48)
		CML	Japanese	Pop-PK	34 (13/16/5)	CL/F	NS	(49)
CYP3A4	–392A>G; *1B (rs2740574)	GIST	Caucasian	Cross-sectional	70 (64/6/0)	CL/F	NS	(47)
		GIST (adult & paediatric)	Caucasian	Pop-PK	46 (16 adult) (42/3/1)	CL/F	NS	(17)
	878T>C; *18; L293P (rs28371759)	CML	Korean	Cross-sectional	82 (77/5/0)	Css	NS	(48)
CYP3A5	6986A>G; *3 (rs776746)	GIST	Korean	Cross-sectional	209 (13/68/128)	Css	NS	(50)
		CML	Korean	Cross-sectional	82 (3/27/52)	Css	NS	(48)
		CML	Japanese	Cross-sectional	62 (W+H 22/40)	Css	NS	(51)
		CML	Japanese	Pop-PK	34 (2/12/20)	CL/F	NS	(49)
		CML	Asian (84:11:5 Chinese: Indian: Malay)	Cross-sectional	38 (2/18/18)	Css	NS	(52)
		GIST	Caucasian	Cross-sectional	79 (0/13/57)	CL/F	NS	(47)
		GIST (adult & paediatric)	Caucasian	Pop-PK	46 (16 adult) (2/8/36)	CL/F	NS	(17)
		GIST + CML	Caucasian + non-Caucasian (>30%)	Pop-PK	21 (0/5/16)	CL/F	NS	(36)

NDIM, N-desmethyl imatinib; Css, steady-state trough total plasma concentration (dose-adjusted where appropriate); NS, not significant (point-wise P>0.05); CL/F, apparent oral total plasma imatinib clearance; CML, chronic myeloid leukaemia; GIST, gastrointestinal stromal tumour; W, n homozygous wild-type genotype; H, n heterozygous genotype; V, n homozygous variant genotype.

investigating whether drug transporter genetic variability influences imatinib disposition. These have either studied genotype differences in the dose-plasma imatinib concentration relationship directly, or intracellular imatinib concentrations tenuously via genotype associations with treatment response. Each of these aspects of imatinib transporter pharmacogenetics is therefore discussed separately.

Effect of transporter genetics on plasma imatinib concentrations and clearance

Pharmacogenetic studies investigating the effect of drug transporter gene polymorphisms on plasma imatinib concentration and clearance are summarised in *Tables 3-5*.

Three major polymorphisms of *ABCB1* (1236C>T, 2677G>T and 3435C>T) have been investigated with respect to imatinib disposition, either individually or as a haplotype (*Table 3*). The expected functional consequences of these polymorphisms for imatinib are not necessarily clear from *in vitro* and clinical studies of other substrates, although variant *ABCB1* genotypes and haplotypes at these loci are typically expected to result in decreased transporter expression (3435C>T) and/or decreased function (1236C>T, 2677G>T, 3435C>T) (72,73). They have therefore been hypothesised to reduce imatinib clearance. However, nearly all studies have found no significant effect of *ABCB1* genotype or haplotype on plasma imatinib concentrations or clearance (*Table 3*).

In a small (n=21) mixed ethnicity and combined CML and GIST patient population, Gurney and colleagues [2007] reported reduced imatinib steady-state clearance estimates for variant *ABCB1* 1236C>T and 3435C>T genotypes. The proposed mechanism was a reduced imatinib clearance from first dose to steady-state in *ABCB1* wild-type, but not variant, patients. However, the 1236C>T association would not be significant after a Bonferroni adjustment for multiple testing [4 *ABCB1* and *CYP3A5* polymorphisms were investigated in the study (36)], and these positive findings have not been replicated in multiple larger studies. Only two other studies have reported a significant *ABCB1* genotype or haplotype effect, and these have been contradictory to the findings of Gurney *et al.* [2007]. The *ABCB1* 3435C>T variant allele has been linked to reduced imatinib clearance in Japanese CML patients (49), whilst variant *ABCB1* haplotypes have been linked to increased likelihood of plasma imatinib concentrations greater than 1,000 ng/mL in Caucasian CML patients (66). Again, neither of these findings would be significant if adjustments were made for multiple comparisons within the respective studies (*Table 3*).

Results have been similar for *ABCG2*, with predominantly negative findings, particularly when accounting for multiple testing within studies (*Table 4*).

The best characterised polymorphisms in *ABCG2* are the non-synonymous 421C>A (Q141K) and 34G>A (V12M), both of which have been investigated for their effect on imatinib disposition. The *ABCG2* 421C>A polymorphism affects the ATP-binding site of the transporter leading to altered transport of some substrates (74), however no genotype differences in plasma imatinib concentrations or clearance have been found among Korean, Indian or Chinese patients (*Table 4*). Petain *et al.* [2008] reported reduced imatinib clearance for the 421 C/A genotype among a combined adult and paediatric Caucasian GIST patient population; however this would not have been statistically significant after adjustment for multiple testing (17). An earlier larger study in Caucasian GIST patients by Gardner *et al.* [2006] also found no significant *ABCG2* 421C>A genotype difference in imatinib clearance (47). Findings in Japanese patients have been mixed, with one study reporting increased plasma imatinib concentrations in *ABCG2* 421A carriers (51), and one reporting no genotype difference in imatinib clearance, albeit with a smaller sample size (n=34) (49).

The *ABCG2* 34G>A polymorphism causes an amino acid change in the N-terminal intracellular region of the transporter, although the functional consequences of this change appear to be minor (74). Reflecting this, no significant *ABCG2* 34G>A genotype differences in plasma imatinib concentrations were observed among 209 Korean GIST patients (50).

Aside from the well-studied ABCB1 and ABCG2 efflux transporters, a single cross-sectional study in 62 Japanese CML patients found no significant *ABCC2* (MRP2 efflux transporter) 24C>T (rs717620) genotype difference in plasma imatinib concentrations (51). There have also been predominantly negative findings for the influx (uptake) transporter genes (*SLC22A1*, *SLC22A2*, *SLCO1A2*, *SLCO1B1* and *SLCO1B3*) investigated to date (*Table 5*), reflecting a lack of evidence for their significant role in imatinib transport.

Effect of transporter genetics on imatinib intracellular distribution

No studies have directly investigated whether transporter genetics influence imatinib concentrations within

Table 3 Effects of ABCB1 efflux drug transporter genetics on plasma imatinib concentrations and clearance

Gene	SNP/haplotype	Patients	Ethnicity	Study design	N (W/H/V)	PK measure	Result	Reference
ABCB1	1236C>T (rs1128503)	GIST	Korean	Cross-sectional	209 (35/94/80)	Css	NS	(50)
		CML	Korean	Cross-sectional	82 (17/37/28)	Css	NS	(48)
		CML	Caucasian	Cross-sectional	84 (W+H 64/20)	Css (mean, <> 1000 ng/mL)	NS[a]	(66)
		CML	Caucasian	Pop-PK	60 (27/23/10)	Css, CL/F	NS	(18)
		GIST (adult & paediatric)	Caucasian	Pop-PK	46 (16 adults) (11/26/9)	CL/F	NS	(17)
		GIST + CML	Caucasian + non-Caucasian (>30%)	Pop-PK	21 (3/8/10)	CL/F	Gene-dose: T/T 25%> C/T 9%> C/C (P=0.02)[†]	(36)
		CML	Japanese	Cross-sectional	62 (W+H 32/30)	Css	NS	(51)
		CML	Japanese	Pop-PK	34 (5/19/10)	CL/F	NS	(49)
		CML	Asian (84:11:5 Chinese: Indian: Malay)	Cross-sectional	38 (6/11/21)	Css	NS	(52)
	2677G>T; A893S (rs2032582)	GIST	Korean	Cross-sectional	209 (41/135/33)	Css	NS	(50)
		CML	Caucasian	Cross-sectional	79 (29/34/16)	Css (mean, <> 1,000 ng/mL)	NS	(66)
		CML	Caucasian	Cross-sectional	82 (62/13/7)	Css	NS	(67)
		CML	Caucasian	Pop-PK	60 (26/23/11)	Css, CL/F	NS	(18)
		GIST (adult & paediatric)	Caucasian	Pop-PK	46 (16 adult) (14/26/6)	CL/F	NS	(17)
		GIST + CML	Caucasian + Non-Caucasian (>30%)	Pop-PK	21 (4/9/8)	CL/F	NS	(36)
		CML	Indian	Cross-sectional	73 (7/H+V 66)	Css	NS	(68)
		CML	Japanese	Cross-sectional	62 (10/34/18)	Css	NS	(51)
		CML	Japanese	Pop-PK	34 (10/14/10)	CL/F	NS	(49)
		CML	Asian (84:11:5 Chinese: Indian: Malay)	Cross-sectional	30 (14/10/6)	Css	NS	(52)

Table 3 (*continued*)

Table 3 (*continued*)

Gene	SNP/haplotype	Patients	Ethnicity	Study design	N (W/H/V)	PK measure	Result	Reference
ABCB1	3435C>T (rs1045642)	GIST	Korean	Cross-sectional	209 (81/98/30)	Css	NS	(50)
		CML	Korean	Cross-sectional	82 (35/38/9)	Css	NS	(48)
		CML	Caucasian	Cross-sectional	89 (16/46/27)	Css (mean, <>1,000 ng/mL	NS	(66)
		GIST	Caucasian	Cross-sectional	82 (21/41/20)	CL/F	NS	(47)
		CML	Caucasian	Cross-sectional	84 (27/31/26)	Css	NS	(67)
		CML	Caucasian	Pop-PK	60 (18/31/11)	Css, CL/F	NS	(18)
		GIST (adult & paediatric)	Caucasian	Pop-PK	46 (16 adult) (14/24/8)	CL/F	NS	(17)
		GIST + CML	Caucasian + non-Caucasian (>30%)	Pop-PK	21 (3/10/8)	CL/F	Gene-dose: T/T 28% > C/T 15% > C/C (P<0.01)	(36)
		CML	Indian	Cross-sectional	73 (11/H+V 62)	Css	NS	(68)
		CML	Japanese	Cross-sectional	62 (15/37/10)	Css	NS	(51)
		CML	Japanese	Pop-PK	34 (7/21/6)	CL/F	T carriers: 38% ↓ (P=0.04)[†]	(49)
		CML	Asian (84:11:5 Chinese: Indian: Malay)	Cross-sectional	38 (13/15/10)	Css	NS	(52)
	1236/3435	CML	Korean	Cross-sectional	82	Css	NS	(48)
	1236/2677/3435	CML	Caucasian	Cross-sectional	85	Css (<> 1,000 ng/mL)	TTC or TTT carrier: OR =2.6 Css >1,000 ng/mL *vs.* non-carriers (P=0.046)[†]	(66)
		CML	Caucasian	Pop-PK	60	Css, CL/F	NS	(18)
		GIST (adult & paediatric)	Caucasian	Pop-PK	46 (16 adult)	CL/F	NS	(17)
		CML	Asian (84:11:5 Chinese: Indian: Malay)	Cross-sectional	38	Css	NS	(52)

[†], would not be significant after correction for multiple comparisons (point-wise P>0.01 from >30 (49), ≥10 (66), or 4 (36) different genotype/haplotype combinations investigated); [a], published P values for 1236C>T genotype differences in Css <>1,000 ng/mL incorrect (or frequencies incorrectly reported). Css, steady-state trough total plasma concentration (dose-adjusted where appropriate); CL/F, apparent oral total plasma imatinib clearance; NS, not significant (point-wise P>0.05); CML, chronic myeloid leukaemia; GIST, gastrointestinal stromal tumour; W, n homozygous wild-type genotype; H, n heterozygous genotype; V, n homozygous variant genotype.

Table 4 Effects of ABCG2 efflux drug transporter genetics on plasma imatinib concentrations and clearance

Gene	SNP/haplotype	Patients	Ethnicity	Study design	N (W/H/V)	PK measure	Result	Reference
ABCG2	34G>A; V12M (rs2231137)	GIST	Korean	Cross-sectional	209 (119/75/15)	Css	NS	(50)
	421C>A; Q141K (rs2231142)	GIST	Korean	Cross-sectional	209 (103/88/18)	Css	NS	(50)
		CML	Korean	Cross-sectional	82 (41/32/8)	Css	NS	(48)
		CML	Indian	Cross-sectional	73 (55/H+V 18)	Css	NS	(68)
		CML	Japanese	Cross-sectional	62 (41/H+V 21)	Css	A carriers: 36% ↑ (P=0.015)[†]	(51)
		CML	Japanese	Pop-PK	34 (21/13/0)	CL/F	NS	(49)
		GIST	Caucasian	Cross-sectional	82 (66/16/0)	CL/F	NS	(47)
		GIST (adult & paediatric)	Caucasian	Pop-PK	46 (16 adult) (41/5/0)	CL/F	C/A: 23% ↓ (P<0.05)[†]	(17)
		CML	Asian (84:11:5 Chinese: Indian: Malay)	Cross-sectional	38 (19/7/2)	Css	NS	(52)

[†], Would not be significant after correction for multiple comparisons [point-wise P>0.01 from ≥10 (17,51) different genotype/haplotype combinations investigated]. Css, steady-state trough total plasma concentration (dose-adjusted where appropriate); CL/F, apparent oral total plasma imatinib clearance; NS, not significant (point-wise P>0.05); CML, chronic myeloid leukaemia; GIST, gastrointestinal stromal tumour; W, n homozygous wild-type genotype; H, n heterozygous genotype; V, n homozygous variant genotype.

patients' CML cells. Whilst Nambu and colleagues [2011] investigated associations between *SLC22A1*, *SLCO1B1*, *SLCO1B3*, *ABCB1* and *ABCG2* polymorphisms and leukocyte intracellular imatinib concentrations in CML patients, patient cells were isolated 3 to 84 (median 19) months into treatment when CML cells make up only a small fraction of circulating cells, and there were no significant genotype differences after accounting for multiple testing (point-wise P≥0.02 from six different polymorphisms and multiple endpoints) (75).

Rather than investigating intracellular distribution directly, previous studies have instead assessed whether transporter genotypes differ in various measures of treatment response. Findings of individual studies investigating the *ABCB1* 1236C>T, 2677G>T and 3435C>T polymorphisms have been inconsistent and often contradictory, whilst *ABCG2* 421C>A variant genotypes have generally been associated with either improved or no difference in treatment response (40). Reflecting this, meta-analyses suggest that the *ABCG2* 421C>A, and less so *ABCB1*, polymorphisms correlate with imatinib response, at least in Asian CML patients (76-78). Where polymorphisms in uptake transporter genes (*SLC22A1*, *SLCO1A2*, *SLCO1B3*) have been investigated in multiple studies, the clear majority of findings are negative (40). An exception is the *SLC22A4* 1507C>T polymorphism, which has been associated with poorer treatment response [reduced likelihood of major molecular response (79), and shorter time to disease progression (80)] in two separate studies of Caucasian CML patients.

Unfortunately, despite conclusions often drawn from reported transporter genotype-response relationships, study design limitations have meant that they do not provide strong evidence for a genetic mechanism of variable imatinib intracellular distribution. This is because almost none have controlled for potential genotype effects on plasma imatinib concentrations [with the exception of Vine *et al.* 2014 (67)], or quantified intracellular imatinib concentrations. Therefore, where genotype correlations with treatment response are identified, it is unknown if this is due to genotype effects on the dose-plasma concentration relationship, genotype effects on imatinib intracellular distribution, or possibly neither (e.g., due to spurious associations, or potential genotype effects on CML pathology unrelated to imatinib disposition, particularly with respect to transporters lacking good evidence for imatinib transport). Without demonstrating a feasible underlying mechanism(s), and hence whether

Table 5 Effects of uptake drug transporter genetics on plasma imatinib concentrations and clearance

Gene	SNP/haplotype	Patients	Ethnicity	Study design	N (W/H/V)	PK measure	Result	Reference
SLC22A1	156T>C (rs1867351)	CML	Japanese	Cross-sectional	62 (27/28/7)	Css	NS	(51)
	181C>T; R61C (rs12208357)	GIST	Caucasian	Cross-sectional	74 (67/6/1)	CL/F	NS	(69)
		CML	Caucasian	Pop-PK	60 (53/6/1)	Css, CL/F	NS	(18)
	480C>G; L160F (rs683369)	CML	Caucasian	Cross-sectional	84 (50/27/7)	Css	NS	(67)
		CML	Caucasian	Pop-PK	60 (35/21/4)	Css, CL/F	G carriers: 18% ↓ CL/F (P<0.0001)	(18)
		CML	Japanese	Cross-sectional	62 (39/H+V 23)	Css	NS	(51)
	1022C>T; P341L (rs2282143)	CML	Japanese	Cross-sectional	62 (37/25/0)	Css	NS	(51)
		CML	Japanese	Pop-PK	34 (24/8/2)	CL/F	NS	(49)
		CML	Indian	Cross-sectional	73 (59/H+V 14)	Css	NS	(68)
	1260_1262delGAT; M420del (rs72552763)	CML	Caucasian	Pop-PK	60 (41/16/3)	Css, CL/F	NS	(18)
	1222A>G; M408V (rs628031)	CML	Japanese	Cross-sectional	62 (W+H 27/35)	Css	NS	(51)
		CML	Indian	Cross-sectional	73 (12/H+V 61)	Css	NS	(68)
		CML	Caucasian	Cross-sectional	83 (33/40/10)	Css	NS	(67)
	1386C>A; (rs622342)	CML	Indian	Cross-sectional	73 (6/H+V 67)	Css	NS	(68)
	1393G>A; G465R (rs34059508)	GIST	Caucasian	Cross-sectional	74 (73/0/1)	CL/F	NS	(69)
	181/1260_1262/480	CML	Caucasian	Pop-PK	60	Css, CL/F	NS	(18)
	24 tag-SNP haplotype	CML	Asian (84:11:5 Chinese: Indian: Malay)	Cross-sectional	38	Css	IVS6-878C>A; 1222A>G; IVS7+850C>T sub-haplotype: 2 copies of AGT and/or CGC haplotype 50% ↑ (P=0.013)[†]	(52)
SLC22A2	808G>T; S270A (rs316019)	CML	Korean	Cross-sectional	82 (67/15/0)	Css	NS	(48)

Table 5 (*continued*)

Table 5 (*continued*)

Gene	SNP/haplotype	Patients	Ethnicity	Study design	N (W/H/V)	PK measure	Result	Reference
SLCO1A2	−1105G>A; (rs4148977)	CML	Japanese	Pop-PK	34 (18/12/4)	CL/F	NS	(70)
	−1032G>A; (rs4148978)	CML	Japanese	Pop-PK	34 (18/12/4)	CL/F	NS	(70)
	−361G>A; (rs3764043)	CML	Japanese	Pop-PK	34 (21/12/1)	CL/F	A carriers: 39% ↑ (P=0.005)	(70)
	38T>C; I13T (rs10841795)	GIST	Caucasian	Cross-sectional	94(58/35/1)	CL/F	NS	(71)
	502C>T; R168C (rs11568564)	GIST	Caucasian	Cross-sectional	94[a]	CL/F	NS	(71)
	516A>C; E172D (rs11568563)	GIST	Caucasian	Cross-sectional	94 (87/6/1)	CL/F	NS	(71)
	968T>C; L323P (rs11568579)	GIST	Caucasian	Cross-sectional	94[a]	CL/F	NS	(71)
	1063A>G; I355V (rs45628437)	GIST	Caucasian	Cross-sectional	94[a]	CL/F	NS	(71)
SLCO1B1	521T>C; V174A (rs4149056)	CML	Japanese	Pop-PK	34 (26/7/1)	CL/F	NS	(49)
SLCO1B3	334T>G; S112A (rs4149117)	CML	Japanese	Cross-sectional	62 (8/22/32)	Css	NS	(51)
		CML	Japanese	Pop-PK	34 (5/10/19)	CL/F	G/G 36% ↑ (P=0.019)[†]	(49)

[†], Would not be significant after correction for multiple comparisons [point-wise P>0.01 from >30 (49,52) different genotype/haplotype combinations investigated]. a, Genotype numbers not published. Css, steady-state trough total plasma concentration (dose-adjusted where appropriate); CL/F, apparent oral total plasma imatinib clearance; NS, not significant (point-wise P>0.05); CML, chronic myeloid leukaemia; GIST, gastrointestinal stromal tumour; W, n homozygous wild-type genotype; H, n heterozygous genotype; V, n homozygous variant genotype.

dose adjustment might be of benefit, it is not reasonable to make personalised dosing recommendations based on these associations alone.

Summary of pharmacogenetic studies

CYP2C8 genotype was recently found to significantly affect imatinib metabolism and consequently imatinib exposure in CML patients; a novel finding awaiting replication. Alternatively, multiple studies clearly demonstrate that the *CYP3A5*3* polymorphism has no significant effect on imatinib pharmacokinetics clinically. The imatinib efflux transporters ABCB1 and ABCG2 have been well represented in imatinib pharmacogenetic research, whilst many studies have also been devoted to genes encoding transporters with little evidence for, or with evidence against, imatinib transport. Regardless, transporter genetic variability appears to have no reproducible effect on plasma imatinib concentrations or clearance. Whilst the *ABCG2* 421C>A variant appears to be associated with improved treatment outcomes in Asian CML patients, the mechanism of this association is unknown, and study design limitations have meant that very little is known about whether transporter genetic variability affects imatinib distribution into patients' CML cells *in vivo*.

Future directions

A potential caveat to concluding that CYP3A5 and transporter genetics do not influence plasma imatinib concentrations or clearance is that nearly all studies [bar (50)] have been conducted with relatively small sample sizes [median n=68 (range, 21–94)], and all without exception have measured total plasma concentrations likely to be confounded by variability in plasma protein binding. Therefore, these studies have

generally lacked sufficient statistical power. In addition to the potential application of meta-analyses to existing imatinib pharmacogenetic data, it is important that future prospective studies are sufficiently powered, particularly taking into account statistical multiple testing.

In order to establish whether genetics influence imatinib intracellular distribution and thus the plasma concentration-response relationship, it should first be demonstrated that an *in vivo* CML cell intracellular concentration-response relationship exists; at present this relationship is entirely, though soundly, theoretical. Subsequent (or parallel) pharmacogenetic studies will also need to be better designed to include measurements of total plasma imatinib concentrations at a minimum, but ideally unbound plasma and intracellular imatinib concentrations, alongside measures of clinical and molecular response. Our knowledge of genetic risk factors for imatinib adverse effects is also currently limited, with few pharmacogenetics studies having incorporated measures of imatinib toxicity or related dose reduction (10,36,68,81), and no significant findings to date.

In addition to replicating findings for *CYP2C8*, other novel candidate genes may also warrant investigation. For example, the *POR* gene encodes the cytochrome p450 oxidoreductase (POR) that provides electrons for microsomal cytochrome P450 metabolism, and the common *POR*28* variant has a significant effect on POR activity (82-84). Polymorphisms in genes encoding the nuclear receptors that regulate expression of drug metabolizing enzymes and transporters (e.g., *NR1I2*, *NR1I3*, *NR1H4*, *NR3C1*, *HNF4A*, *VDR*, *PPARG*) may also be important, and have previously been linked to altered pharmacokinetics of other drugs (85). Although, a small cross-sectional study in 38 mixed ethnicity CML patients found no significant effect of *NR1I2* polymorphisms on plasma imatinib concentrations (52).

The identification of the major imatinib uptake transporter(s) will also be of significant importance to our understanding of imatinib disposition, and might also be a source of genetic variability contributing to variable imatinib pharmacokinetics and treatment response.

In moving toward developing tools to improve personalised imatinib dosing, it will also be important to consider integrating pharmacogenetic testing and potential therapeutic drug monitoring or target concentration intervention approaches.

Conclusions

In conclusion, *CYP2C8* genotype has a potentially clinically relevant effect on the imatinib dose-plasma concentration relationship, and warrants further investigation. Other drug metabolism and transport genes investigated to date have little or no effect on imatinib clearance. The genetic influence on imatinib intracellular distribution is currently unknown due to major study design limitations. Therefore, whilst potential genetic influences on plasma imatinib exposure have been identified, evidence is still lacking to support a role of pharmacogenetics in personalised imatinib dosing.

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