Drug Transporters and Imatinib Treatment: Implications for Clinical Practice

Karel Eechoute¹, Alex Sparreboom¹,², Herman Burger¹, Ryan M. Franke², Gaia Schiavon¹, Jaap Verweij¹, Walter J. Loos¹, Erik A.C. Wiemer¹, and Ron H.J. Mathijssen¹

Abstract

Imatinib mesylate is approved for the treatment of chronic myeloid leukemia (CML) and advanced gastrointestinal stromal tumors (GIST). Unfortunately, in the course of treatment, disease progression occurs in the majority of patients with GIST. Lowered plasma trough levels of imatinib over time potentially cause disease progression, a phenomenon known as “acquired pharmacokinetic drug resistance.” This outcome may be the result of an altered expression pattern or activity of drug transporters. To date, the role of both efflux transporters (ATP-binding cassette transporters, such as ABCB1 and ABCCG2) and uptake transporters [solute carriers such as organic cation transporter 1 (OCT1) and organic anion transporting polypeptide 1A2 (OATP1A2)] in imatinib pharmacokinetics and pharmacodynamics has been studied. In vitro experiments show a significant role of ABCB1 and ABCCG2 in cellular uptake and retention of imatinib, although pharmacokinetic and pharmacogenetic data are still scarce and contradictory. ABCB1 and ABCC1 expression was shown in GIST, whereas ABCB1, ABCCG2, and OCT1 were found in mononuclear cells in CML patients. Several studies have reported a clinical relevance of tumor expression or activity of OCT1 in CML patients. Further (clinical) studies are required to quantify drug transporter expression over time in organs involved in imatinib metabolism, as well as in tumor tissue. In addition, more pharmacogenetic studies will be needed to validate associations.

Introduction

Imatinib mesylate (Gleevec, Novartis International AG) is the first approved rationally designed inhibitor of specific protein tyrosine kinases. The drug inhibits ABL and the BCR-ABL fusion protein [expressed in Philadelphia chromosome–positive chronic myeloid leukemia (CML)], c-KIT [expressed in gastrointestinal stromal tumors (GIST)], and the platelet-derived growth factor receptor (PDGF-R; i.e., expressed in some sarcomas; refs. 1–4). Imatinib has become the standard treatment for patients with chronic myeloid leukemia (5, 6) and GIST (7–10).

Although response rates in imatinib-treated patients are high, ranging between 70 to 90% of patients with GIST as well as CML (9, 11, 12), nonresponse or disease progression after a certain period of time may occur. Genetic mutations or gene amplification of the drug targets are known mechanisms for this observed (acquired) drug resistance (12–15). Accumulating data, however, indicate a contributing role of pharmacokinetics in imatinib efficacy, as well as for the initial therapeutic response, and for the time to progression. Drug uptake and efflux transporters are likely to be involved in imatinib absorption, distribution, and excretion, thereby influencing pharmacokinetics. Imatinib is almost completely absorbed (>97%; ref. 16) and is, then, extensively metabolized in the liver with CGP74588 as its most active metabolite, predominantly formed by cytochrome P450 isoform 3A4 and 3A5 (CYP3A4, CYP3A5) as shown in Fig. 1 (17). This metabolite is equipotent to its parental compound in vitro. Other cytochrome P450 isoforms (CYP1A2, CYP2D6, CYP2C8, CYP2C9, and CYP2C19) also play a (minor) role in imatinib metabolism (17, 18). At clinically relevant concentrations, imatinib is bound to plasma proteins, mainly albumin and α1-acid glycoprotein (16, 19). Both imatinib and its active metabolite are excreted in feces and, to a lesser extent, in urine.

Initial drug resistance could be correlated with drug exposure. For instance, imatinib trough levels, the lowest drug concentration, right before administration of a new dose, in nonresponding patients are significantly lower (see Table 1) than in responding patients (20–22). Moreover, imatinib pharmacokinetics may also contribute to acquired drug resistance. This finding was shown in a small-population pharmacokinetics study in patients with GIST (23). After long-term treatment (>1 year), imatinib clearance increased by ≈33% and systemic exposure decreased by ≈42%, compared with the start of treatment, possibly suggesting involvement of pharmacokinetics in the...
Interaction of Imatinib with Drug Transporters

**Efflux transporters.** Imatinib is a substrate of ATP-binding cassette (ABC) transporters such as the ABC subfamily B member 1 (ABCB1; formerly known as P-glycoprotein or MDR1; refs. 32–38) and subfamily G member 2 (ABCG2; formerly known as breast cancer resistance protein [BCRP]; refs. 37, 39, 40), which are involved in its excretion process. These drug transporters use the hydrolysis of ATP and subsequent phosphorylation of the transporter as an energy source, enabling active transport of substrates across various biomembranes (41, 42). Studies have reported imatinib as an inhibitor of ABC transporters (35, 43, 44), but there is growing consensus that ABC transporter inhibition by imatinib is dose dependent with inhibition only occurring at higher imatinib concentrations (Table 2; refs. 35, 37, 38). ABCB1 and ABCG2 are expressed in a variety of tissues, including liver (at the sinusoidal basolateral membrane, as well as the apical bile canalicular membrane of hepatocytes; refs. 1, 37, 45, 46), intestine (at the apical membrane; see Fig. 1; refs. 45–47), kidney, placenta (46, 48), and the blood-brain barrier (41, 49). The role of these efflux transporters in acquired drug resistance has been investigated more intensively than the role of uptake transporters because of the evident physiologic role of efflux transporters as a defense mechanism against penetration of xenobiotics.

**Uptake transporters.** Meanwhile, more than one fourth of the present-day anticancer drugs are oral formulations, stressing the possible relevance of intestinal absorption through uptake transporters expressed on the apical membrane of enterocytes. These solute carriers (SLC) use electrochemical gradients of ions to transport substrates across a membrane. Mainly the role of organic cation transporter 1 (OCT1 or the SLC22A1 gene product) and to a lesser extent organic anion transporting polypeptide 1A2 (OATP1A2, the SLC21A6 gene product) in imatinib uptake has been described (50, 51). Furthermore, imatinib proved to be a good substrate for the solute carriers OATP1B3 (SLCO1B3 gene product) and OCTN2 (SLC22A5 gene product), both expressed on the basolateral membrane of hepatocytes (Fig. 1; ref. 51).

**Drug Transporters and Imatinib Pharmacokinetics**

**Absorption**

This knowledge raises the question whether altered pharmacokinetics can be (in part) the result of (over) expression of drug transporters. At duodenal pH 5 to 6, imatinib is mainly charged (52), implying active intestinal transport; this renders intestinally located solute carriers such as OATP1A2 and OCTN2 as good candidates for intestinal imatinib uptake (53, 54). However, to date, little is known about the influence of these uptake transporters on imatinib pharmacokinetics. Another good candidate for systemic imatinib uptake is ABCC4, expressed on the basolateral membrane of hepatocytes (51). This efflux transporter could pump imatinib from the liver to the systemic circulation.

As mentioned above, imatinib is absorbed very efficiently, which is somewhat surprising, considering the high affinity of imatinib for ABC transporters, expressed on the canalicular membrane of hepatocytes and on enterocytes. A possible explanation for this apparent contradiction could be local substrate inhibition of efflux transporters by imatinib, bearing in mind its...
dose-dependent interaction. Furthermore, absolute bioavailability could also be influenced by the balance between efflux and influx transport over the intestinal barrier, favoring active imatinib uptake.

**Tissue distribution**

*Liver distribution.* Imatinib is actively cleared from the blood into the liver, where it is metabolized extensively. Possible candidates for this active transport are OATP1B3, OCTN2, and OCT1, predominantly located at the basolateral membrane of hepatocytes (Fig. 1; refs. 16, 51, 55, 56).

However, *in vivo* or clinical data, supporting the role of solute carriers in imatinib clearance, are not available.

*Brain distribution.* Systemic treatment of brain tumors (primary as well as metastases) is limited because of low penetration of drugs into the brain tissue. Distribution to the brain is primarily prevented by the blood-brain barrier formed by the endothelial cells of brain capillaries. These endothelial cells also express ABCB1 and ABCG2 (41, 49), which actively prevent xenobiotics from diffusing into the brain. This finding was illustrated in Bcrp and Mdr1a/1b (rodent analogs of ABCG2 and ABCB1, respectively).
Table 1. Imatinib trough levels (Cmin) in imatinib-treated chronic myeloid leukemia and gastrointestinal stromal cell tumor patients with or without clinical response

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Dose range (mg)</th>
<th>No. of patients</th>
<th>No. of responders</th>
<th>Mean or median Cmin in responders (ng/mL)</th>
<th>Median free Cmin in responders (ng/mL)</th>
<th>No. of nonresponders</th>
<th>Mean or median Cmin in nonresponders (ng/mL)</th>
<th>Median free Cmin in nonresponders (ng/mL)</th>
<th>P-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML</td>
<td>400–800</td>
<td>351</td>
<td>297</td>
<td>1,009 (± 544)(^{a,b})</td>
<td>n.a.(^{c})</td>
<td>54</td>
<td>812 (± 409)(^{a})</td>
<td>n.a.(^{c})</td>
<td>0.01</td>
<td>20</td>
</tr>
<tr>
<td>CML</td>
<td>50–800</td>
<td>254</td>
<td>218</td>
<td>1,057 (± 585)(^{a,b})</td>
<td>n.a.(^{c})</td>
<td>36</td>
<td>835 (± 524)(^{a})</td>
<td>n.a.(^{c})</td>
<td>0.033</td>
<td>30</td>
</tr>
<tr>
<td>CML</td>
<td>50–800</td>
<td>254</td>
<td>166</td>
<td>1,107 (± 594)(^{a,d})</td>
<td>n.a.(^{c})</td>
<td>88</td>
<td>873 (± 528)(^{a})</td>
<td>n.a.(^{c})</td>
<td>0.002</td>
<td>30</td>
</tr>
<tr>
<td>CML</td>
<td>400–600</td>
<td>68</td>
<td>56</td>
<td>1,123 (± 617)(^{a,b})</td>
<td>n.a.(^{c})</td>
<td>12</td>
<td>694 (± 556)(^{a})</td>
<td>n.a.(^{c})</td>
<td>0.03</td>
<td>21</td>
</tr>
<tr>
<td>CML</td>
<td>400–600</td>
<td>68</td>
<td>34</td>
<td>1,452 (± 649)(^{a,d})</td>
<td>n.a.(^{c})</td>
<td>34</td>
<td>869 (± 427)(^{a})</td>
<td>n.a.(^{c})</td>
<td>0.001</td>
<td>21</td>
</tr>
<tr>
<td>GIST(^{i})</td>
<td>Not reported</td>
<td>33</td>
<td>14</td>
<td>2,340 (± 520)(^{a,a})</td>
<td>n.a.(^{c})</td>
<td>20</td>
<td>690 (± 150)(^{a})</td>
<td>n.a.(^{c})</td>
<td>0.002</td>
<td>29</td>
</tr>
<tr>
<td>GIST(^{i})</td>
<td>Not reported</td>
<td>73</td>
<td>57</td>
<td>1,446 (414–3,336)(^{a,g})</td>
<td>n.a.(^{c})</td>
<td>16</td>
<td>1,155 (545–4,182)(^{a,h})</td>
<td>n.a.(^{c})</td>
<td>0.25</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations: CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumors.

\(^{a}\) Mean Cmin (±SD).

\(^{b}\) Response is defined as complete cytogenetic response.

\(^{c}\) Not available.

\(^{d}\) Response is defined as major molecular response.

\(^{e}\) Response is defined as complete hematologic response at 3 months or major cytogenetic response at 6 months.

\(^{f}\) Median Cmin (and range).

\(^{g}\) Response is defined by the response evaluation criteria in solid tumors (RECIST) as stable disease, partial response or complete response.

\(^{h}\) Nonresponse is defined as disease progression by RECIST or not assessable.

\(^{i}\) Patients with exon 9 mutated or wt KIT GIST.

\(^{j}\) Median free Cmin (and range) deduced from imatinib and AGP levels.

\(^{k}\) Nonresponse is defined by RECIST as disease progression.
knockout mouse models, showing that imatinib brain penetration significantly increased in knockout mice compared with wild-type mice, with a greater difference in Mdr1a/1b knockout (57). Another study with a rodent model showed that combined Bcrp and Mdr1a/1b knock- out proved to significantly increase brain penetration compared with individual Bcrp or Mdr1a/1b knockouts (33). These data suggest that inhibition of efflux transporters at the blood-brain barrier may provide more tools in the treatment of brain metastases in imatinib-treated patients.

A few obstacles remain, however. For instance, Gardner and colleagues showed that inhibition of ABCB1 and ABCG2 in mice resulted in a proportional increase in systemic exposure to imatinib in plasma and brain, leaving the brain-to-plasma concentration ratio unaltered (58). This finding suggests that reduced systemic elimination of imatinib leads to the observed increase in imatinib exposure to the brain as a result of higher imatinib concentrations at the blood-brain barrier, rather than a modification of the barrier itself. Furthermore, it is still unclear if efflux inhibitors will increase imatinib levels in tumor cells located in the central nervous system, because these inhibitors may be merely increasing brain uptake of substrates but not necessarily uptake into brain tumors (39).

Excretion

**Biliary secretion.** Up until now, in vivo experiments on the importance of drug transporters for imatinib excretion have shown only minor effects. Systemic clearance of imatinib in Mdr1a/1b and Bcrp1 knockout mice was 1.3-fold and 1.6-fold lower than wild-type mice (57). A combined Mdr1a/1b/Bcrp1 knockout showed a 1.8-fold reduction in imatinib plasma clearance compared with wild-type mice when imatinib was administered intravenously (33). Interestingly, no differences in pharmacokinetic parameters were found between Mdr1a/1b/Bcrp knockout and wild-type mice after oral administration of imatinib. Whether ABCB1 and ABCG2 contribute to imatinib clearance in humans to a similar degree and, more importantly, whether there is a possible upregulation of these efflux transporters in excretory organs during imatinib treatment is unknown. These murine data, however, suggest a minor contribution of efflux transporters to imatinib clearance, compared with the hepatic metabolism. Indeed, an extensive first-pass metabolism of imatinib could contribute more substantially to systemic clearance than Mdr1a/1b and Bcrp1 efflux.

Furthermore, protein expression of Abcb1 and Bcrp1 in mice did not differ after long-term treatment with orally

---

**Table 2. Interaction between drug transporters and imatinib pharmacokinetics and pharmacodynamics**

<table>
<thead>
<tr>
<th>Drug transporter</th>
<th>Study design</th>
<th>Effects on imatinib PK</th>
<th>Effects on imatinib PD</th>
<th>Transporter interaction</th>
<th>Effect on imatinib IUR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1</td>
<td>In vitro</td>
<td></td>
<td>Resistance ↑</td>
<td></td>
<td>IUR ↑</td>
<td>34–35,39</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td>Systemic clearance ↑</td>
<td></td>
<td></td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>In vivo</td>
<td></td>
<td></td>
<td></td>
<td>Systemic clearance ↑</td>
<td>33,57</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Inhibitor</td>
<td>32,40</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Substrate</td>
<td>32,35,37</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37–38</td>
</tr>
<tr>
<td>ABCG2</td>
<td>In vitro</td>
<td></td>
<td>Systemic clearance ↑</td>
<td></td>
<td>IUR =</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>No resistance</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>In vivo (mice)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33,57</td>
</tr>
<tr>
<td></td>
<td>In vivo (mice)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>In vivo (mice)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Inhibitor</td>
<td>37,43–44</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Inducer</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>In vivo (mice)</td>
<td></td>
<td></td>
<td></td>
<td>No inducer</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Substrate</td>
<td>37–39</td>
</tr>
<tr>
<td>OCT1</td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>IUR =</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50,62</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td>Resistance ↓</td>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Clinical (CML)</td>
<td>63,65–66</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td>Resistance ↓</td>
<td></td>
<td></td>
<td>63,65–66</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Substrate</td>
<td>50,62</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Substrate</td>
<td>51</td>
</tr>
<tr>
<td>OATP1A2</td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Substrate</td>
<td>51</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Substrate</td>
<td>51</td>
</tr>
<tr>
<td>OCTN2</td>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td>Substrate</td>
<td>51</td>
</tr>
</tbody>
</table>

Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics; IUR, intracellular uptake and retention.
administered imatinib (60). After daily administration for 4 consecutive weeks, no upregulation of Abcb1 and Bcrp1 in mouse liver and intestinal tissues was found. Also, no significant change in plasma and liver concentrations of imatinib was seen. Theoretically, however, the length of treatment required to induce upregulation of these drug transporters in mice might be longer or the activity of both efflux transporters over the course of time may change without a quantitative change in expression.

Renal excretion. Although renal excretion accounts for less than 10% of imatinib excretion (31, 61), increased plasma exposure and decreased clearance in imatinib-treated cancer patients with impaired renal function, were seen (61). This finding may be due to increased levels of circulating uremic toxins. One such toxin inhibits Oatp1b3 function in a rodent model (55), supporting the possibility that uremic toxins can directly reduce hepatic uptake of imatinib by Oatp1b3. Further elucidation of this mechanism is needed.

Drug Transporters and Imatinib Pharmacodynamics

Role of OCT1 in chronic myeloid leukemia blasts. There is substantial evidence that tumor OCT1 expression or activity determines therapeutic outcome in imatinib-treated CML patients. Thomas and colleagues were the first to show that inhibition of OCT1 in peripheral blood leukocytes from 6 CML patients, decreased intracellular imatinib uptake (62). This finding was confirmed in another study, showing that imatinib uptake in a CML cell line significantly correlated with OCT1 mRNA expression (63). Furthermore, White and colleagues showed that in vitro sensitivity for imatinib strongly correlated with the intracellular uptake and retention of imatinib in mononuclear cells of untreated CML patients (50). When prazosin, an OCT1 inhibitor, was added to these cells, the concentration needed to inhibit molecular drug targets was significantly increased. Furthermore, it was also shown that only the activity of OCT1 in mature CML blasts is associated with therapeutic outcome and the OCT1 activity in immature CD34+ cells (64). This could imply that effective tumoral uptake of imatinib by OCT1 may be decisive for therapeutic response in CML patients. On the other hand, Hu and colleagues showed that intracellular uptake of imatinib in (nonleukemic) cells overexpressing OCT1 was only minimally higher than in control cells (51). In a gene expression analysis, they showed that Slc22a1 is significantly interrelated with Abcb1, ABCG2, and Slco1a2. Alternatively, Slc22a1 gene expression could, therefore, be a marker for expression and subsequent activity of other transporters involved in imatinib transport.

SLC22A1 gene expression did prove to be a good predictor of clinical outcome in imatinib-treated CML patients (63, 65). Pretreatment OCT1 expression levels in 32 CML patients were 8 times higher in responders than in nonresponding patients (65). This result was confirmed in 70 CML patients, in which high baseline OCT1 RNA expression levels correlated with better cytogenetic response at 6 months and prolonged progression-free and overall survival (63). White and colleagues showed that chronic phase CML patients with low OCT1 activity showed clinical benefit from imatinib dose escalation, but they reported no correlation between clinical efficacy and OCT1 mRNA levels (66).

ABC transporter expression in gastrointestinal stromal tumor and chronic myeloid leukemia. ABCB1 and ABCC1 are expressed in approximately three quarters of GISTs, which is 2- to 3-fold more than the expression in leiomyosarcomas (67–69). On the other hand, Western blot analysis of 21 GIST specimens showed no expression of ABCG2 (68). So, in contrast to the possible influence of ABCG2 on the intestinal uptake of imatinib (33, 40, 57), there seems to be no role for ABCG2 on a tumoral level in GIST patients. Little can be said of the impact of ABCB1 and ABCC1 expression in stromal tumor cells on imatinib therapy in these GIST patients because only a very limited number of patients in these studies were treated with imatinib.

Although preclinical data (34–36) show that cellular (over) expression of ABCB1 leads to a reduced intracellular accumulation of imatinib, it is not clear whether long-term treatment with imatinib induces overexpression of this transporter in tumor cells. Mahon and colleagues examined various cell lines and found no upregulation of the expression of the ABCB1 gene by imatinib in time (70). In contrast, bone marrow mononuclear cells in CML patients resistant to imatinib showed an overexpression of ABCB1 and ABCG2 (although not statistically significant; ref. 65). In addition, a gene expression analysis in CML patients showed that expression of ABCC3 in CML blasts was unique to patients with disease recurrence (71). More studies with larger populations are needed to elucidate the possible tumoral upregulation of efflux transporters during imatinib therapy and its pharmacodynamic effects.

Integrating Knowledge of Transporters in Improving Imatinib Therapy: Pharmacogenetic Studies

Pharmacokinetic impact of genetic variation in ABC transporters. To date, pharmacogenetic association studies were predominantly done for ABCB1 and ABCG2 (Table 3). Associations between 2 single nucleotide polymorphisms, known to reduce the activity of ABCB1 and ABCG2, respectively, and steady state imatinib pharmacokinetics in 82 patients with mainly GIST, have been investigated (72). Sixteen patients had a heterozygous variant (421 C > A) genotype for ABCG2 and 20 patients expressed a homozygous variant for ABCB1 3435 C > T. No significant differences in imatinib pharmacokinetics were seen compared with the homozygous wild-type patients. On the other hand, Takahashi and colleagues recently showed that imatinib trough levels were significantly higher in CML patients carrying an ABCG2 421A allele (in homozygous as well as heterozygous variant genotypes; ref. 73).
Gurney and colleagues found that patients with a TTT haplotype in \textit{ABCB1}1236C > T, 2677G > T/A, and 3435 C > T loci had significant higher estimated imatinib clearances (74). This finding is contradictory to reports showing lower mRNA and protein levels when a homozygous T allele for \textit{ABCB1}3435C > T was present (75), and to the findings of others who observed a decreased hepatic \textit{99m}TC-MIBI elimination rate, a phenotypic marker for \textit{ABCB1}-mediated drug clearance, in patients with the TTT haplotype (76). In addition, in CML patients, a TTT-haplotype was associated with higher imatinib trough levels (77).

**Clinical impact of genetic variation in \textit{ABCB1} transporters.** Up until now, pharmacogenetic association studies assessing clinical efficacy were exclusively done in CML patients. A poor response was observed in CML patients who were homozygous for the G allele in \textit{ABCG2}34G > A (78). As for \textit{ABCB1}, a 1236T allele was associated with better response, whereas a 2677G allele or a CGC haplotype for the 1236, 2,677, and 3,435 loci were associated with worse response in CML patients (77). However, Kim and colleagues observed a reduced overall survival in CML patients carrying a TT genotype for 3435C > T locus, when analyzed univariately (78). This finding was confirmed by another group, who observed more resistance in CML patients carrying T alleles at positions 1236 and 3,435 (79). All in all, data on the role of pharmacogenetics in response and survival in CML patients receiving imatinib therapy are scarce and poorly validated or reproduced.

**Pharmacokinetic and clinical impact of genetic variations in solute carriers.** To date, studies assessing the possible role of genetic polymorphisms in solute carriers in imatinib therapy are limited to OCT1 and OATP1B3. Allelic variants of the \textit{SLC22A1} gene (encoding for the OCT1 protein) with known reduced function showed no effect on steady state

<table>
<thead>
<tr>
<th>Transporter gene</th>
<th>Polymorphism</th>
<th>Effects on imatinib PK</th>
<th>Effects on imatinib PD</th>
<th>No. of patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{ABCB1}</td>
<td>3435 T</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>82</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>3435 T</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>TTT haplotype(^{c})</td>
<td>Clearance ↑</td>
<td>Overall survival ↓ (^{d})</td>
<td>90</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>3435 T</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Resistance ↑ (^{e})</td>
<td>22</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>1236 T</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Resistance ↑ (^{e})</td>
<td>90</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>1236 T</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>2677 T/A</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>2677 G</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>90</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>CGC haplotype(^{c})</td>
<td>Response = (^{b} )</td>
<td>Response = (^{b} )</td>
<td>90</td>
<td>77</td>
</tr>
<tr>
<td>\textit{ABCG2}</td>
<td>421 A</td>
<td>No</td>
<td>Response = (^{b} )</td>
<td>82</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>421 A</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>34 A</td>
<td>No</td>
<td>Response = (^{b} )</td>
<td>229</td>
<td>78</td>
</tr>
<tr>
<td>\textit{ABCG2}</td>
<td>–24 T</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td>\textit{SLC22A1}</td>
<td>181 T</td>
<td>SS imatinib plasma level =</td>
<td>74</td>
<td>74</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>1393 A</td>
<td>SS imatinib plasma level =</td>
<td>74</td>
<td>74</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>181 T</td>
<td>Response = (^{b} )</td>
<td>Response = (^{b} )</td>
<td>32</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>480 G</td>
<td>Response = (^{b} )</td>
<td>Response = (^{b} )</td>
<td>229</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>1022 T</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>1222 G</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>156 C</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>334 G</td>
<td>( C_{\text{min}} = ^{a} )</td>
<td>Response = (^{b} )</td>
<td>67</td>
<td>73</td>
</tr>
</tbody>
</table>

Abbreviations: PK, pharmacokinetics; PD, pharmacodynamics; SS, steady state.

\(^{a}\)Imatinib plasma trough level.

\(^{b}\)Major molecular response.

\(^{c}\)Description haplotype: 1236C > T, 2677G > T/A, 3435C > T.

\(^{d}\)Defined as the period from initiation of imatinib therapy until the date of death from any cause or the date of last follow-up.

\(^{e}\)Nonresponse defined as absence of cytogenetic response.

\(^{f}\)Major or complete cytogenetic response.

\(^{g}\)Higher rate of loss of cytogenetic or molecular response.
imatinit plasma levels (181C>T and 1393G>A), in a group of GIST and CML patients compared with the reference genotype (51). Furthermore, Zach and colleagues found no significant differences in response in patients heterozygous for the T allele in the SLC22A1 181C>T polymorphism (80). Also, no correlation between SLC01B3 334T > G polymorphism and imatinib exposure or clinical response was seen in CML patients (73). On the other hand, CML patients carrying a homozygous GG genotype for the SLC22A1 480C > G polymorphism showed a lower response rate (78). Furthermore, a higher response rate was seen in CML patients carrying a GG genotype for the 1222A>G locus (73). Unfortunately, imatinib trough levels did not significantly differ for these patients, carrying a 1222GG genotype, as compared with the reference allele.

Future Perspectives

Although in vitro studies show that imatinib exposure leads to an upregulation of ABCB1 and ABCC2 in human colon carcinoma cells (40), currently no data are available on the expression of these drug transporters in human intestinal cells under imatinib therapy. Future studies should assess the possible correlation between their expression pattern in excretory organs over time with imatinib pharmacokinetics and clinical outcome. In order to study the role of these transporters in the observed decline in imatinib clearance, a series of intestinal biopsies at different time points are needed.

Current studies also show that the majority of GIST expresses both ABCB1 and ABCC1, but its clinical importance is not yet elucidated. Although tumor expression of OCT1 in CML patients has already been correlated with therapeutic outcome, more data are needed on the expression pattern of drug transporters in tumor cells in both CML and GIST patients and their possible pharmacodynamic impact. At least a quantification of these transporters over time should be made in GIST biopsies or mononuclear cells in CML patients in order to assess the possibility of an altered expression pattern of drug transporters as a mechanistic explanation for an altered sensitivity to the drug.

Finally, pharmacogenetic association data will need to be validated or reproduced. At this point, no clear guidelines exist on the design of pharmacogenetic studies. Preventing selection bias, adequate power analysis, clear endpoints, correction for genetic and nongenetic covariates, and other factors are often poorly implemented. Therefore, more pharmacogenetic studies assessing the association with imatinib pharmacokinetics and/or pharmacodynamics are desired, and study design will need to be uniform. In the present context of rapidly emerging promising compounds, the latter is of utmost importance if we want to personalize dosing and treatment sequences of rationally designed molecules to an individual patient's needs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received August 21, 2010; revised November 2, 2010; accepted November 12, 2010; published OnlineFirst December 16, 2010.

References

Drug Transporters and Imatinib Treatment


37. Shukla S, Sauna ZE, Ambudkar SV. Evidence for the interaction of imatinib at the transport-substrate site(s) of the multidrug-resistance-linked ABC drug transporters ABCB1 (P-glycoprotein) and ABCG2. Leukemia 2008;22:445–52.


and brain penetration of imatinib mesylate (Gleevec); implications for the use of breast cancer resistance protein and P-glycoprotein inhibitors to enable the brain penetration of imatinib in patients. Cancer Res 2005;65:2577–82.


Drug Transporters and Imatinib Treatment: Implications for Clinical Practice

Karel Eechoute, Alex Sparreboom, Herman Burger, et al.

Clin Cancer Res  Published OnlineFirst December 16, 2010.

Updated version  Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-10-2250

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.