**Introduction**

Imatinib mesylate (IM), a tyrosine kinase inhibitor, is one of the first molecularly targeted therapies to have been used in the clinic. It has proven to be efficient in the treatment of chronic myeloid leukemia and also in other malignancies that involve expression of a tyrosine kinase. However, some patients can develop resistance and others suffer from toxic side effects. The pharmacokinetics of IM depends on several enzymes and transporters, and several studies have attempted to identify genetic factors associated with variable drug levels and clinical responses using a candidate gene approach. Larger and more homogenous studies are still needed to replicate the findings obtained so far, or to analyze other genetic variations to get clearer insights into how IM treatment can be tailored to each patient’s genetics. Here we summarize pharmacogenetic studies of IM and highlight the genetic markers that could be used to improve the treatment and management of diseases for which IM is used.

**Abstract**

Imatinib mesylate (IM), a tyrosine kinase inhibitor, is one of the first molecularly targeted therapies to have been used in the clinic. It has proven to be efficient in the treatment of chronic myeloid leukemia and also in other malignancies that involve expression of a tyrosine kinase. However, some patients can develop resistance and others suffer from toxic side effects. The pharmacokinetics of IM depends on several enzymes and transporters, and several studies have attempted to identify genetic factors associated with variable drug levels and clinical responses using a candidate gene approach. Larger and more homogenous studies are still needed to replicate the findings obtained so far, or to analyze other genetic variations to get clearer insights into how IM treatment can be tailored to each patient’s genetics. Here we summarize pharmacogenetic studies of IM and highlight the genetic markers that could be used to improve the treatment and management of diseases for which IM is used.

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**The pharmacogenetics of imanitib**

Stéphanie Dulucq1 and Maja Krajinovic2*

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**Introduction**

Imatinib mesylate (IM, also known as STI571, Glivec or Gleevec) is a competitive tyrosine kinase inhibitor commonly used for treatment of chronic myeloid leukemia (CML). It has also proven efficient for the treatment of advanced gastrointestinal stromal tumors (GISTs), c-KIT mastocytosis and myeloproliferative disorders with rearrangement of the platelet derived growth factor receptor (PDGFR) gene. In CML, IM inhibits the tyrosine kinase activity of the fusion protein of breakpoint cluster region (BCR) gene and the ABL tyrosine kinase (BCR-ABL), which results from a t(9;22)(q34,q11) translocation known as the Philadelphia chromosome; this fusion protein has a role in leukemogenesis [1]. IM occupies the ATP-binding pocket of the ABL kinase domain; this prevents a change in conformation of the protein that would otherwise convert the molecule to its active form, and IM binding thereby leads to the apoptosis of target cells.

Three main criteria can be used to evaluate the response to CML treatment: complete hematological remission, defined as a normal peripheral blood count with normal spleen; complete cytogenetic response (CCyR), defined by absence of the Philadelphia chromosome in bone marrow metaphase analysis; and major molecular response (MMR), defined by the thousand-fold (3 log) reduction in BCR-ABL transcript levels relative to the standardized baseline [1]. Other levels of cytogenetic or molecular response can be used [1], as mentioned in Table 1. Despite outstanding results of IM in the treatment of chronic phase CML, some patients do not achieve response criteria (for example, about 25% of patients did not achieve CCyR at 18 months [2], and some patients (about 25%) who initially responded well subsequently acquired resistance [3]. Apart from dosage errors, drug interactions and non-compliance with treatment, several mechanisms can contribute to the development of resistance: changes to the target protein (occurring through mutations or BCR-ABL amplification); downstream BCR-ABL-independent pathways; and drug pharmacokinetics parameters (absorption, distribution, metabolism and excretion). In malignancies other than CML, IM inhibits the tyrosine kinase domains of KIT and PDGFRA/β. Myeloproliferative disorders with PDGFR rearrangement show great sensitivity to IM and mostly require a lower dose of IM; this is especially true of chronic eosinophilic leukemia, which involves a fusion transcript of FIP1-like1 and PDGFRA [4]. In mastocytosis, the overall response rate varies according to c-KIT mutational status and has been reported to be 18 to 36% [5]. In GISTs, IM leads to a response rate of 50 to 70%, with a 2-year overall survival rate of 70% [6].

In the conventional dose range, a fourfold inter-patient variability has been reported both in the systemic exposure for a given dose and in the dose required to achieve a specific target level [7]. Variation in drug concentration may result in excessive toxicity or suboptimal anticancer effect. Reduced IM efficacy has been
| Genes | SNP*      | Base substitution† | Functional effect‡ | No of patients | Response criteria | IM dosage | Association | References |
|-------|-----------|--------------------|-------------------|----------------|------------------|-----------|------------|------------|
| ABCB1 | rs1128503 | C1236T             | +                 | 90 French      | MMR at 12 months | 400 mg    | Higher MMR with 1236T allele | [20]       |
|       | -         | 62 Japanese        |                   | 229 Canadian   |                  |           | No         |            |
|       | -         | 87 English         |                   | 46 Dutch       | Cumulative incidence of MMR and CMR at 12 months | 800 mg   | No         | [24]       |
|       | -         | 557 French         |                   |                |                  | 400 mg, 400 mg + IFN 400 mg + AraC; 600 mg | No         | [21]       |
|       | -         | 52 Chinese         |                   |                |                  | 400 mg    | Lower CCyR with TT genotype | [23]       |
|       | -         | 52 Chinese         |                   |                |                  | 400 mg, 400 mg + IFN 400 mg + AraC; 600 mg | No         | [21]       |
|       | -         | 52 Chinese         |                   |                |                  | 400 mg    | Higher MMR with 2677G allele | [20]       |
|       | rs2032582 | G2677T/A           | +                 | 90 French      | MMR at 12 months | 400 mg    | Overall survival lower with TT genotype but not confirmed in multivariate analysis | [25]       |
|       | -         | 62 Japanese        |                   | 229 Canadian   |                  |           | No         |            |
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|       | -         | 52 Chinese         |                   |                |                  | 400 mg    | Higher CCyR with AG/AT/AA genotypes | [23]       |
|       | rs1045642 | C3435T*            | -                 | 90 French      | MMR at 12 months | 400 mg    | No         | [20]       |
|       | -         | 62 Japanese        |                   | 229 Canadian   |                  |           | No         | [26]       |
| ABCB1 | rs1045642 | C3435T*            |                   | 229 Canadian   | CyR and MR at 1, 1.5, 2, 3, 4 and 5 years† | 400, 600 or 800 mg | Overall survival lower with TT genotype but not confirmed in multivariate analysis | [25]       |
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|       | -         | 52 Chinese         |                   |                |                  | 400 mg    | Higher CCyR with CC genotype | [23]       |
| ABCG2 | rs717620  | C421A*             | -                 | 62 Japanese    | MMR               | ≥400 and ≤300 mg | No         | [26]       |
|       | rs2231142 | C421A*             | +                 | 62 Japanese    | MMR               | ≥400 and ≤300 mg | No         | [26]       |
|       |           | 229 Canadian       |                   |                | CyR and MR at 1, 1.5, 2, 3, 4 and 5 years† | 400, 600 or 800 mg | Higher CMR with AA genotype; more frequent need for IM dose escalation for CC genotype | [25]       |
| SLC22A1| rs12208357| G34A               |                   | 229 Canadian   | CyR and MR at 1, 1.5, 2, 3, 4 and 5 years† | 400, 600 or 800 mg | Lower MCyR and CCyR with GG genotypes | [25]       |

Continued overleaf
linked to low drug exposure; the main reported toxicities of IM are neutropenia, superficial edema, nausea, muscle cramps and rashes [1-3]. Trough IM plasma levels (C_{min}) have been reported to be associated with MMR in CML patients following standard drug dose [8,9]. A plasma threshold of 1,002 ng/ml had the best sensitivity and specificity to predict MMR [8]. Patients with C_{min} below this threshold have less chance to achieve MMR compared with patients with C_{min} above it. Likewise, higher circulating levels of IM correlated with a better response rate and with a longer time to progression in patients with advanced GISTs with C_{min} of more than 1,100 ng/ml [10].

Observed inter-patient pharmacokinetic variability may be due to patients’ genetics. Polymorphisms in genes related to IM absorption, distribution, metabolism and excretion may affect the drug’s bioavailability and consequently the response to the drug. The oral bioavailability of IM depends on its gastrointestinal absorption and on how much of it survives the extensive first pass metabolism that it encounters. Approximately 95% of IM in the human body is bound to plasma proteins,
mainly serum albumin and α1 acid glycoprotein (AGP). Removal of IM is mediated by the P glycoprotein (P-gp, also called ABCB1 or MDR1) and breast cancer resistance protein (BCRP), and uptake is mediated by human organic cation transporter 1 (hOCT1). IM is mostly metabolized by the cytochrome P450 (CYP) proteins CYP3A4 and CYP3A5 [11]. Various studies have analyzed the polymorphisms in genes encoding these proteins in relation to IM pharmacokinetics and response, as detailed below and in Table 1.

**Overview of pharmacogenetic studies**

**Pharmacokinetic determinants**

Cancer cells have the ability to become resistant to multiple different drugs known as the multi drug resistance (MDR) phenomenon. This is due, among other mechanisms, to increased transport of drugs out of the cell. Mahon et al. [12] showed that IM is a substrate of P-gp and could thus be affected by MDR. This was confirmed by the facts that CML patients who did not achieve a CCyR had higher levels of expression of ABCB1 and that there was a correlation between pharmacokinetics and response, as detailed below and in Table 1.

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[35,36]. For example, the Arg61Cys, Cys88Arg and Gly401Ser amino acid replacements resulting from the corresponding genetic polymorphisms were shown to affect the transport of hOCT1 substrates [30]. Bazeos et al. [37] identified an association between Gly401Ser substitution (G1201A, rs34130495) and the transcription level of the SLC22A1 gene (Table 1). In addition, CML patients with the 1201GA genotype had higher probability of achieving MMR than patients with the 1201GG genotype. These results, however, need to be confirmed in a larger cohort given the low frequency of the A allele. Indeed, White et al. [38] were not able to replicate this finding. Kim et al. [25] showed instead that the SLC22A1 C480G polymorphism (rs683369), which leads to Leu160Phe replacement, is associated with IM response in CML. Patients with the 480GG genotype showed a higher risk of treatment failure or loss of response than other genotypes. Finally, Takahashi et al. [26] showed that the SLC22A1 A1222G polymorphism (rs628031), which leads to Met408Val replacement, is associated with molecular response in the group of patients treated with IM doses lower than 400 mg. Patients with the 1222GG genotype showed a higher MMR rate.

Uptake of imatinib has also been described, in vitro, to be mediated to a modest extent by SLCO1B3, which encodes the organic anion-transporting polypeptide 1B3 [39], but Takahashi et al. [26] did not find any association with IM response (Table 1).

Metabolizing enzymes
Among CYP3A5 polymorphisms, the CYP3A5*3 allele is particularly interesting, as it appears with a sufficiently high frequency and has a clear functional role. The CYP3A5*3 allele is defined by the A6986G substitution (rs776746), which generates a cryptic splice site and the introduction of a premature stop codon [40]. Individuals who are homozygous for this allele have reduced CYP3A5 levels and reduced metabolic capacity. In the study of Kim et al. [25], the 6986AA genotype had an adverse impact on achievement of CCyR, whereas Takahashi et al. [26] did not find an association between this allele and dose-adjusted IM trough concentration or clinical response (Table 1). In contrast, Sailaja et al. [41] found a higher frequency of the 6986GG genotype in CML patients with a minor or poor hematological response.

Binding proteins
The role of AGP in the mechanisms of IM resistance is not yet clear [42]. In GIST patients, an association was found between high plasma AGP levels and a lower clearance of IM and its metabolite [43]. Kim et al. [25] did not observe any association between AGP polymorphisms and IM response in CML patients.

Pharmacodynamic determinants
IM tyrosine kinase targets represent potential pharmacodynamic determinants. Any modification in these targets could modulate the efficacy of IM and affect its mechanism of action.

Acquired point mutations in the tyrosine kinase domain of BCR-ABL are the most frequent mechanism of acquired resistance to IM in CML [44]. These mutations should be distinguished from the polymorphisms in the ABL gene that could be responsible for primary resistance. However, their role is not yet clear. For example, the Lys247Arg amino acid replacement resulting from an adenine-to-guanine substitution does not seem to be functional [45]. Ernst et al. [46] found six different polymorphisms in CML patients with failure of treatment or suboptimal IM response, but the clinical impact of these variations still needs to be investigated.

Approximately 95% of GIST patients express the receptor tyrosine kinase KIT and 86% of GISTs contain c-KIT activating mutations that lead to a ligand-independent activation of the tyrosine kinase. These somatic mutations mostly occur in the juxtamembrane domain (encoded by exon 11) and extracellular domains (exon 9). The target kinase mutations in exon 11 are associated with a better overall partial response rate using standard Southwest oncology group response criteria [47].

Some GIST patients without c-KIT mutations show alterations in the juxtamembrane domain (encoded by exon 12) or activation loop domain (exon 18) of PDGFRα, with those with exon 18 mutations having a poor response to IM [47]. Resistance due to the somatic mutations in the tyrosine kinase domain of PDGFRα has also been described in a few cases of chronic eosinophilic leukemia [48]. IM-associated edema is believed to involve a disruption of PDGF signaling. The role of PDGFR polymorphisms in the risk of developing severe edema during IM treatment from CML was analyzed by Bruck et al. [49], but no significant association was found.

Dressman et al. [50] analyzed the effect of 68 polymorphisms in 26 genes on the cytogenetic response to IM. They found a significant association between the rs2290573 polymorphism located in an intron of a putative tyrosine kinase gene, DKK2P4434C131, and the major cytogenetic response (MCyR) in a subset of IM-treated patients. Patients homozygous for the C allele had a significantly lower MCyR rate and a higher risk of disease progression than patients with other genotypes. It is unknown whether this polymorphism has a functional effect or whether it is a genetic marker in linkage disequilibrium with another polymorphism that is functional.

A substantial proportion of patients with IM resistance do not have BCR-ABL tyrosine kinase domain mutations, suggesting the involvement of additional mechanisms in
IM resistance. Activation of other signaling pathways when IM blocks the BCR-ABL-mediated pathway might facilitate cell death avoidance in CML [51]. Recently, Kim et al. [51] analyzed a variety of polymorphisms in the genes of the apoptosis, angiogenesis, cell growth, Wilms tumor gene or interferon (IFN) signaling pathways in CML patients. An association obtained both in test and validation cohorts is particularly interesting. The CC genotype of the rs2069705 polymorphism in the IFNG (IFN-γ) gene was associated with a higher rate of molecular and cytogenetic response, suggesting a potential involvement of the IFN-γ signaling pathway in the mechanism of IM action in CML.

**Clinical relevance of the pharmacogenetics of IM**

Given that there is a large variability in response rate and IM systemic exposure following a standard drug dose, pharmacogenetic studies may provide insights into the role of genetic components in this variability. Focusing on a variety of genes whose products are essential for IM levels and action, these studies may identify potential pharmacokinetic and/or pharmacodynamic markers of IM response. These markers, complementing existing ones such as drug plasma concentrations, could allow the prediction, for each individual, of a lack of efficacy or excess toxicity, leading first to pharmacogenetically guided prospective clinical trials and ultimately to personalized treatment. Pharmacogenetic IM studies have been conducted so far mainly in patients diagnosed with CML or GIST, probably because of the higher incidence of these two diseases. The efficacy and toxicity of IM seem to depend on both IM pharmacokinetics, influenced by several enzymes and transporters, and IM pharmacodynamics, influenced by mutational status of the target. Several polymorphisms affecting the pharmacokinetic determinants of IM have been identified. Nevertheless, the data are not yet sufficiently conclusive to translate into individual drug dose adjustment (several reasons for this are outlined below). Meanwhile, trough IM plasma levels could help physicians to define the best IM dose [8]. In addition, the determination of hOCT1 activity before initiation of IM therapy may also be helpful [38].

**Concluding remarks**

Despite several groups attempting to demonstrate the impact of candidate gene polymorphisms, conflicting results remain. These discrepancies could be explained, at least in some cases, by different response criteria, study sample size, IM dosage and treatment protocols. Most studies have focused on ABCB1 polymorphisms, and constitutive or compensatory changes in expression of other ABC transporters, or IM-induced changes in ABCB1 expression, may confound the observed results in these studies. The results are not always supported by the expected functional effect of a given polymorphism, and they still require replication. It will be necessary to target other genotypes beyond those already analyzed to more comprehensively estimate the effect of the genes from the analysis of both individual polymorphisms and haplotypes.

It seems clear that the effect of IM depends on several genes. An approach involving multiple candidate genes may thus give the benefit of including the potential effects of gene-gene interactions, but this has not been much explored and usually requires larger studies. Further studies are clearly needed to elucidate the real impact of candidate gene polymorphisms on the IM response and to what extent the use of second generation tyrosine kinase inhibitors (nilotinib and dasatinib) may eventually overcome the resistance imposed by certain genetic variations.

**Abbreviations**

AGP, α1 acid glycoprotein; BCRP, breast cancer resistance protein; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; Cmin, trough imatinib plasma level; CMR, complete molecular response; CYP, cytochrome; GIST, gastrointestinal stromal tumor; hOCT1, human organic cation transporter 1; IM, imatinib mesylate; MCIr, major cytogenetic response; MDR, multidrug resistance; MMR, major molecular response; PDGF, platelet-derived growth factor receptor; P-gp, P glycoprotein; SNP, single nucleotide polymorphism.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

Both authors contributed equally to the writing of the manuscript.

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**References**

1. Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silver RT, Goldman J, Hehlmann R, European LeukemiaNet: Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 2009, 27:6041-6051.

2. O’Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen J, Rousselot P, Reff ers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ, IRIS Investigators: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003, 348:994-1004.

3. Hochhaus A, Kreil S, Corbin AS, La Rosee P, Muller MC, Lahaye T, Hanfstein B, Schoch C, Cross NC, Berger U, Gschaidmeier H, Druker BJ, Hehlmann R: Molecular and chromosomal mechanisms of resistance to imatinib (STI571) therapy. Leukemia 2002, 16:2190-2196.
Resistance gene MDRI (ABCB1) predict for molecular resistance in patients with newly diagnosed chronic myeloid leukemia (CML) receiving high-dose imatinib. Blood, 2011, 116:6144-5.

3. Ni LN, Li FS, Mao KR, Qiao G, Zhang SJ, Qu HR, Qian SX: Multidrug resistance gene (MDRI) polymorphisms correlate with imatinib resistance in chronic myeloid leukemia. *Med Oncol* 2011, 24:1702-1706.

4. Marin D, Baezos A, Mahon FX, Ellasson L, Miljkovic D, Bua M, Apperley JF, Szydlo R, Desai R, Kozovsky K, Palompiess C, Latham V, Foron I, Molimard M, Reid A, Rezvani K, de Lavallade H, Guallar C, Goldman J, Khorashad JS: Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukaemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol* 2010, 28:2381-2388.

5. Kim EH, Srinath S, Xu W, Kamei-Heid S, Liu X, Simmouitch V, Messner HA, Lipton JH: Clinical relevance of a pharmacogenetic approach using multiple candidate genes to predict response and resistance to imatinib therapy in chronic myeloid leukemia. *Clin Cancer Res* 2009, 15:4750-4758.

6. Takahashi N, Miura M, Scott SA, Kayaga Y, Kameoka Y, Tagawa H, Saitoh H, Fujishima N, Yoshioka T, Hikawa M, Sawada K: Influence of CYP3A5 and drug transporter polymorphisms on imatinib trough concentration and clinical response among patients with chronic phase chronic myeloid leukemia. *J Human Genet*, doi:10.1038/jhg.2010.98.

7. Doyle LA, Ross DD: Multidrug resistance mediated by the breast cancer resistance protein BCRP (ABCG2). *Oncogene* 2003, 22:7340-7358.

8. Morselli K, Bibey RW, Ozvets-Lacza C, Honig P, Golgar P, Steadman K, Sarkadi B, Bates SE: Single nucleotide polymorphisms modify the transporter activity of ABCG2. *Cancer Chemother Pharmacol* 2006, 56:161-172.

9. Gardner ER, Burger H, van Schak RH, van Oosterom AT, de Bruijn EA, Guetens G, Prehen H, de Jong FA, Baker SD, Bates SE, Figg WD, Verweij J, Sparreboom A, Noote P: Association of enzyme and transporter genotypes with the pharmacokinetics of imatinib. *Clin Pharmacol Ther* 2006, 80:192-201.

10. Petlin A, Kars thatarath D, Azad J, Chatelut E, Delbaldo C, Geiger B, Barros M, Seregn-Vivien S, Lecesne A, Vassal G: Population pharmacokinetics and pharmacogenetics of imatinib in children and adults. *Clin Cancer Res* 2008, 14:7102-7109.

11. Thomas J, Wang L, Clark RE, Pirmohamed M: Active transport of imatinib into and out of cells: implications for drug resistance. *Blood* 2004, 104:3739-3745.

12. White DL, Saunders VA, Dang P, Engler J, Venables A, Zim S, Zannettino A, Lynch K, Manley PW, Hughes T: Most CML patients who have a suboptimal response to imatinib have low OCT-1 activity: higher doses of imatinib may overcome the negative impact of low OCT-1 activity. Blood 2007, 110:4064-4072.

13. Wang L, Giannoudis A, Lane S, Williamson P, Pirmohamed M, Clark RE: Expression of the uptake drug transporter hOCT1 is an important clinical determinant of the response to imatinib in chronic myeloid leukemia. *Clin Pharmacol Ther* 2008, 83:258-264.

14. Crossman LC, Drucker BJ, Deininger MW, Pirmohamed M, Wang L, Clark RE: hOCT1 and resistance to imatinib. *Blood* 2005, 106:1133-1134; author reply 1134.

15. Kold R, Brinkmann U, Chatena K, Gorbonos D, Gorbolev V, Momihnweg E, Keil A, Eichelbaum M, Koeppel H: Identification of genetic variations of the human organic cation transporter hOCT1 and their functional consequences. *Pharmacogenomics* 2002, 12:591-595.

16. Shu Y, Leabman MK, Feng B, Mangravite LM, Huang CC, Stryke D, Kawamoto M, Johns SJ, DeJong J, Carlson E, Ferrin TE, Herskowitz I, Giacomini KM: Pharmacogenetics Of Membrane Transporters Investigators: Evolutionary conservation predicts function of variants of the human organic cation transporter, OCT1. *Proc Natl Acad Sci USA* 2003, 100:5902-5907.

17. Baezos A, Marin D, Reid AG, Gerrard G, Miljkovic D, May PC, de Lavallade H, Garland P, Rezvani K, Apperley JF, Goldman JM, Foroni I, Khorashad JS: hOCT1 transcript levels and single nucleotide polymorphisms as predictive factors for response to imatinib in chronic myeloid leukemia. *Blood* 2007, 110:4064-4072.

18. White DL, Saunders VA, Dang P, Engler J, Venables A, Zim S, Zannettino A, Lynch K, Manley PW, Hughes T: Most CML patients who have a suboptimal response to imatinib have low OCT-1 activity: higher doses of imatinib may overcome the negative impact of low OCT-1 activity. Blood 2007, 110:4064-4072.

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20. Crossman LC, Drucker BJ, Deininger MW, Pirmohamed M, Wang L, Clark RE: hOCT1 and resistance to imatinib. *Blood* 2005, 106:1133-1134; author reply 1134.

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22. Shu Y, Leabman MK, Feng B, Mangravite LM, Huang CC, Stryke D, Kawamoto M, Johns SJ, DeJong J, Carlson E, Ferrin TE, Herskowitz I, Giacomini KM: Pharmacogenetics Of Membrane Transporters Investigators: Evolutionary conservation predicts function of variants of the human organic cation transporter, OCT1. *Proc Natl Acad Sci USA* 2003, 100:5902-5907.

23. Baezos A, Marin D, Reid AG, Gerrard G, Miljkovic D, May PC, de Lavallade H, Garland P, Rezvani K, Apperley JF, Goldman JM, Foroni I, Khorashad JS: hOCT1 transcript levels and single nucleotide polymorphisms as predictive factors for response to imatinib in chronic myeloid leukemia. *Blood* 2007, 110:4064-4072.

24. White DL, Saunders VA, Dang P, Engler J, Venables A, Zim S, Zannettino A, Lynch K, Manley PW, Hughes T: Most CML patients who have a suboptimal response to imatinib have low OCT-1 activity: higher doses of imatinib may overcome the negative impact of low OCT-1 activity. Blood 2007, 110:4064-4072.

25. Wang L, Giannoudis A, Lane S, Williamson P, Pirmohamed M, Clark RE: Expression of the uptake drug transporter hOCT1 is an important clinical determinant of the response to imatinib in chronic myeloid leukemia. *Clin Pharmacol Ther* 2008, 83:258-264.

26. Crossman LC, Drucker BJ, Deininger MW, Pirmohamed M, Wang L, Clark RE: hOCT1 and resistance to imatinib. *Blood* 2005, 106:1133-1134; author reply 1134.

27. Kold R, Brinkmann U, Chatska N, Gorbunov D, Gorboulev V, Momihnweg E, Keil A, Eichelbaum M, Koeppel H: Identification of genetic variations of the human organic cation transporter hOCT1 and their functional consequences. *Pharmacogenomics* 2002, 12:591-595.

28. Shu Y, Leabman MK, Feng B, Mangravite LM, Huang CC, Stryke D, Kawamoto M, Johns SJ, DeJong J, Carlson E, Ferrin TE, Herskowitz I, Giacomini KM: Pharmacogenetics Of Membrane Transporters Investigators: Evolutionary conservation predicts function of variants of the human organic cation transporter, OCT1. *Proc Natl Acad Sci USA* 2003, 100:5902-5907.

29. Baezos A, Marin D, Reid AG, Gerrard G, Miljkovic D, May PC, de Lavallade H, Garland P, Rezvani K, Apperley JF, Goldman JM, Foroni I, Khorashad JS: hOCT1 transcript levels and single nucleotide polymorphisms as predictive factors for response to imatinib in chronic myeloid leukemia. *Blood* 2007, 110:4064-4072.
40. Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, Watkins PB, Daly A, Wrighton SA, Hall SD, Maurel P, Relling M, Brimer C, Yasuda K, Venkataramanan R, Strom S, Thummel K, Boguski MS, Schuetz E: Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A expression. Nat Genet 2001, 27:383-391.
41. Sailaja K, Rao DN, Rao DR, Vishnupriya S: Analysis of CYP3A5*3 and CYP3A5*6 gene polymorphisms in Indian chronic myeloid leukemia patients. Asian Pac J Cancer Prev 2010, 11:781-784.
42. Jorgensen HG, Elliott MA, Allan EK, Carr CE, Holyoake TL, Smith KD: Alpha1-acid glycoprotein expressed in the plasma of chronic myeloid leukemia patients does not mediate significant in vitro resistance to STI571. Blood 2002, 99:713-715.
43. Delbaldo C, Chatelut E, Re M, Deroussent A, Seronie-Vivien S, Jambu A, Berthaud P, Le Cesne A, Blay J, Vassal G: Pharmacokinetic-pharmacodynamic relationships of imatinib and its main metabolite in patients with advanced gastrointestinal stromal tumors. Clin Cancer Res 2006, 12:6073-6078.
44. Apperley JF: Part I: mechanisms of resistance to imatinib in chronic myeloid leukaemia. Lancet Oncol 2007, 8:1018-1029.
45. Nicolini FE, Chabane K, Cayuela JM, Rousselot P, Thomas X, Hayette S: The role of the K247R substitution in the ABL tyrosine kinase domain in sensitivity to imatinib. Haematologica 2006, 91:137-138.
46. Ernst T, Hoffmann J, Erben P, Hanfrein B, Leitner A, Hehlmann R, Hochhaus A, Muller MC: ABL single nucleotide polymorphisms may masquerade as BCR-ABL mutations associated with resistance to tyrosine kinase inhibitors in patients with chronic myeloid leukemia. Haematologica 2008, 93:1389-1393.
47. Corless CL, Fletcher JA, Heinrich MC: Biology of gastrointestinal stromal tumors. J Clin Oncol 2004, 22:3813-3825.
48. Gotlib J, Cools J: Five years since the discovery of FIP1L1-PDGFRA: what we have learned about the fusion and other molecularly defined eosinophilias. Leukemia 2008, 22:1999-2010.
49. Bruck P, Wassmann B, Lopez ER, Hoezer D, Ottmann OG: Development of hygromas or severe edema during treatment with the tyrosine kinase inhibitor STI571 is not associated with platelet-derived growth factor receptor (PDGFR) gene polymorphisms. Leuk Res 2004, 28:1153-1157.
50. Dressman MA, Malinowski R, McLean LA, Gathmann I, Capdeville R, Hensley M, Polymeropoulos MH: Correlation of major cytogenetic response with a pharmacogenetic marker in chronic myeloid leukemia patients treated with imatinib (STI571). Clin Cancer Res 2004, 10:2265-2271.
51. Kim DH, Kong JH, Byeon JY, Jung CW, Xu W, Liu X, Kamel- Reid S, Kim YK, Kim HJ, Lipton JH: The IFNG (IFN-gamma) genotype predicts cytogenetic and molecular response to imatinib therapy in chronic myeloid leukemia. Clin Cancer Res 2010, 16:5339-5350.
52. Zach O, Krieger O, Fordermayr M, Zellhofer B, Lutz D: OCT1 (SLC22A1) R61C polymorphism and response to imatinib treatment in chronic myeloid leukemia patients. Leuk Lymphoma 2008, 49:2222-2223.
53. Entrez SNP [http://www.ncbi.nlm.nih.gov/sites/entrez?db=snp
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