Genome Medicine

REVIEW

The pharmacogenetics of imanitib

Stéphanie Dulucq[1] and Maja Krajinovic[2]*

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.

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 PDGFRα/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 sub-optimal anticancer effect. Reduced IM efficacy has been

*Correspondence: maja.krajinovic@umontreal.ca
[2]Centre de recherche, CHU Sainte-Justine, Départements de Pédiatrie et Pharmacologie, Université de Montréal, 3175 Côte-Ste-Catherine, Montréal, QC H3T 1C5, Canada
Full list of author information is available at the end of the article

Table 1. Summary of studies of the efficacy of IM treatment in relation to pharmacokinetic genetic variants*

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 in front line or 2nd line after IFN	Higher MMR with 1236T allele	[20]
			-	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	No	[25]
				87 English	MMR¶ at 18 months	400 mg	No	[24]
				46 Dutch	Cumulative incidence of MMR and CMR at 12 months	800 mg	Higher MMR and CMR with CC genotype	[22]
				557 French	MMR at 12 months	400 mg; 400 mg + IFN 400 mg + AraC; 600 mg	No	[21]
				52 Chinese	CCyR at 12 months	400 mg	Lower CCyR with TT genotype	[23]
	rs2032582	G2677T/A	+	90 French	MMR at 12 months	400 mg in front line or 2nd line after IFN	Lower MMR with 2677G allele	[20]
			-	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	No	[25]
				46 Dutch	Cumulative incidence of MMR and CMR at 12 months	800 mg	Lower CMR with TT genotype	[22]
				557 French	MMR at 12 months	400 mg; 400 mg + IFN 400 mg + AraC; 600 mg	Higher MMR with 2677G allele in the arm 400 mg + AraC	[21]
				52 Chinese	CCyR at 12 months	400 mg	Higher CCyR with AG/AT/AA genotypes	[23]
	rs1045642	C3435T¥	-	90 French	MMR at 12 months	400 mg in front line or 2nd line after IFN	No	[20]
			-	62 Japanese	MMR	≥400 and ≤300 mg	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]
				46 Dutch	Cumulative incidence of MMR and CMR at 12 months	800 mg	Lower CMR with TT genotype	[22]
				557 French	MMR at 12 months	400 mg; 400 mg + IFN 400 mg + AraC; 600 mg	No	[21]
				52 Chinese	CCyR at 12 months	400 mg	Higher CCyR with CC genotype	[23]
ABCG2	rs717620		-	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]
	rs2231137	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]
SLC22A1	rs12208357			32 Austrian	MMR at 18 months	400 mg	No	[52]
			-	132 English	MMR	400 mg	No	[37]
				229 Canadian	CyR and MR at 1, 1.5, 2, 3, 4 and 5 years§	400, 600 or 800 mg	No	[25]

Continued overleaf

Table 1. Continued

Genes	SNP*	Base substitution†	Functional effect‡	No of patients	Response criteria	IM dosage	Association	References
			-	136 Australian	MMR at 2 years	<600 mg or ≥600 mg	No	[38]
	rs2282143		-	132 English	MMR	400 mg	No	[37]
			-	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	No	[25]
	rs34130495	G1201A¥	-	132 English	MMR	400 mg	Higher MMR with GA genotypes	[37]
SLC22A1			-	136 Australian	MMR at 2 years	<600 mg or ≥600mg	No	[38]
	rs622342		-	132 English	MMR	400 mg	No	[37]
	rs1867351		-	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	No	[25]
	rs683369	C480G	-	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 risk of loss of response and treatment failure with GG genotypes	[25]
	rs628031	A1222G	-	62 Japanese	MMR	≥400 and ≤300 mg	Higher MMR with GG genotypes	[26]
				229 Canadian	CyR and MR at 1, 1.5, 2, 3, 4 and 5 years§	400, 600 or 800 mg	No	[25]
			-	136 Australian	MMR at 2 years	<600 mg or ≥600mg	No	[38]
	rs 72552763		-	136 Australian	MMR at 2 years	<600 mg or ≥600mg	No	[38]
SLCO1B3	rs4149117		-	62 Japanese	MMR	≥400 and ≤300 mg	No	[26]
CYP3A5	rs776746	A6986G	-	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	Lower MCyR and CCyR with AA genotypes	[25]
				265 Indian	Hematological response (HR)	400 mg	Lower HR with GG genotypes	[41]
	rs28383468			229 Canadian	CyR and MR at 1, 1.5, 2, 3, 4 and 5 years§	400, 600 or 800 mg	No	[25]
AGP	rs3182041			229 Canadian	CyR and MR at 1, 1.5, 2, 3, 4 and 5 years§	400, 600 or 800 mg	No	[25]

*****All patients were in chronic phase except for the study of Kim *et al.* [25], in which 203 patients were in chronic phase and 26 patients in accelerated phase or in blast crisis. †The base substitution and rs number taken from the National Centre for Biotechnology information SNP database [53] are indicated for polymorphisms positively associated with IM response. For the remaining SNPs for which no association was found, only the rs number is indicated. ‡Functional impact *in vivo*: association had been found between polymorphisms and transcript levels of candidate genes or with trough IM concentration. §CyR, cytogenetic response; MR, molecular response; the cumulative incidence of major cytogenetic response (MCyR), CCyR, MMR, complete molecular response (CMR), loss of response, treatment failure and overall survival was measured. ¶MMR in patients with CCyR. ¥Polymorphisms with demonstrated functional effect *in vitro*.

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 *BCR-ABL* and *ABCB1* transcript levels in these patients [13]. However, in GIST patients, the expression level of *ABCB1* did not seem to impair the initial response to IM [14].

ABCB1 contains 28 exons and is located on chromosome 7q21.1. The silent C3435T polymorphism (rs1045642) in exon 26 of *ABCB1* was the first polymorphism to be described; it was reported to modify P-gp expression [15] (Table 1). Decreased substrate specificity, lower levels of intestinal P-gp and reduced levels of *ABCB1* mRNA in 3435TT individuals were reported [15-17]. Consistent with this, increased bioavailability of some P-gp substrates has been observed to be associated with the 3435TT genotype in several studies, although conflicting reports have subsequently appeared showing higher or no correlation with *ABCB1* expression or P-gp activity [18]. The C3435T polymorphism is in linkage disequilibrium with a silent C1236T polymorphism (rs1128503) in exon 12 and a non-synonymous substitution G2677T/A (rs2032582) in exon 21, which leads to an amino acid change of Ala893 to serine or threonine; this may also contribute to the observed functional effect of variation at the C3435T polymorphism or at associated haplotypes.

Gurney *et al.* [19] reported a higher IM clearance in CML and GIST patients with the TT genotype at each of three positions in the *ABCB1* gene (positions 1236, 2677 and 3435). Reduction in dose as a result of toxicity also tended to be less commonly needed in these individuals [19]. We and our colleagues [20] found a higher frequency of MMR in CML patients carrying the 1236T allele and in patients with non-G genotypes at position 2677. However, we could not confirm these results in a larger patient cohort [21]. Only in the subgroup of patients treated with both IM and cytarabine (also called AraC) was an association with the *ABCB1* 2677 polymorphism found, but, contrary to the initial finding [20], the presence of allele 2677G (GA or GG or GT) was associated with a higher rate of MMR [21]. This finding is surprising given that AraC is not a substrate of P-gp. The result is nevertheless similar to that reported by Deenik *et al.* [22], who observed a lower probability of cumulative MMR for CML patients who were homozygous for the *ABCB1* alleles 3435T and 2677T, as well as for those having at least one 1236T allele. Finally, Ni *et al.* [23] reported a higher resistance rate in homozygous *ABCB1* 1236T patients and in those with at least one 3435T allele, whereas better CCyR was observed for patients with the AG/AT/AA genotype at position 2677. Three other studies conducted with CML patients did not find an association between *ABCB1* polymorphisms and MMR [24-26].

BCRP, which, like P-gp, causes removal of IM, is encoded by the *ABCG2* gene located on chromosome 4q22. BCRP is expressed not only in hematopoietic stem cells but also in hepatic and intestinal epithelial cells, and this affects the bioavailability of IM [27]. The SNPs G34A (rs2231137), which substitutes a valine for a methionine, and C421A (rs2231142), which substitutes a glutamine for a lysine, are the most frequent non-synonymous polymorphisms in *ABCG2* across various populations (Table 1) [28]. Experiments *in vitro* using various drug substrates showed that the Gln141Lys substitution affects the transport efficiency of BCRP and may result in altered pharmacokinetics and drug-resistance profiles [28]. Human embryonic kidney cells transfected with the 141Lys variant of BCRP showed greater IM accumulation *in vitro* [29]. Consistent with this, a lower IM clearance and a higher dose-adjusted IM trough concentration were found in CML patients with the 141Lys variant [26,30], whereas the 141Gln variant reduced the response to IM [25]. In addition, the 34GG genotype was associated with a lower frequency of cytogenetic response [25], although the functional effect of this variant is less clear. In contrast to the reports on CML, pharmacokinetic IM parameters were not significantly different across genotypes of Gln141Lys polymorphism in patients with GISTs and KIT-positive soft tissue sarcoma [29].

The hOCT1 protein, encoded by the solute carrier family 22 gene (*SLC22A1*) on chromosome 6q26 [31], may also affect the response to IM by regulating its uptake. CML patients with low hOCT1 activity showed lower probability of achieving MMR [32], whereas those with high baseline level showed better survival and higher probability of achieving a cytogenetic or molecular response [24,33,34]. Given the important predictive role of *SLC22A1* expression, some investigators have focused on gene variations that may affect hOCT1 function

[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 PDGFRA, 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 PDGFRA 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, *DKFZP434C131*, 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; C_{min}, trough imatinib plasma level; CMR, complete molecular response; CYP, cytochrome; GIST, gastrointestinal stromal tumor; hOCT1, human organic cation transporter 1; IM, imatinib mesylate; MCyR, major cytogenetic response; MDR, multidrug resistance; MMR, major molecular response; PDGFR, 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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Author details

[1]Laboratoire Hématopoïèse Leucémique et Cible Thérapeutique, Université Victor Ségalen Bordeaux 2, Inserm U876, CHU Bordeaux, Bordeaux, France. [2]Centre de recherche, CHU Sainte-Justine, Départements de Pédiatrie et Pharmacologie, Université de Montréal, 3175 Côte-Ste-Catherine, Montréal, QC H3T 1C5, Canada.

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