To the editor:

Polymorphisms in the multidrug resistance gene *MDR1* (ABCB1) predict for molecular resistance in patients with newly diagnosed chronic myeloid leukemia receiving high-dose imatinib

Recently, Dulucq and coworkers reported that multidrug resistance gene (*MDR1*) polymorphisms were associated with major molecular responses (MMRs) to standard-dose imatinib in chronic myeloid leukemia (CML).[1] Significantly more patients homozygous for allele 1236T achieved a MMR. Patients with this genotype had also higher imatinib concentrations. These findings suggested a better response in patients with the TT genotype.

We studied the same most prevalent ABCB1 gene single nucleotide polymorphisms (SNPs), C1236T, G2677T/A, and C3435T, with respect to molecular response in a cohort of 46 early chronic phase CML patients receiving high-dose imatinib (800 mg) according to the Hemato-Oncologie voor Volwassenen Nederland (HOVON)–51 protocol.[2,3] No significant differences in baseline characteristics including age, Sokal risk score, and dose of cytarabine were apparent among the different MDR1 genotypes. Genotyping was performed using Taqman allelic discrimination assays on an ABI Prism 7000 Sequence detection system (Applied Biosystems), with 2 allele-specific minor groove binding probes for each SNP. The distribution of the allelic variants of each of the 3 SNPs were in Hardy-Weinberg equilibrium. However, each combination of 2 SNPs was in strong linkage disequilibrium ($P < .001$). The overall incidences of a MMR and complete molecular response (CMR) were, respectively, 78% and 41% at 2 years from diagnosis, after a median follow-up of 46 months (range, 32-60 months). Among the patients homozygous for 1236C, a cumulative incidence of MMR of 92% after 1 year was observed, compared with 52% and 50% in patients with genotype CT or TT, respectively (P = .02; Table 1), which effect remained statistically significant in multivariate analysis. Hazard ratios to achieve a CMR for patients harboring the CT and TT alleles were, in multivariate analysis, respectively, 0.25 (0.10-0.63) and 0.27 (0.08-0.97), $P = .01$, indicating a 4-fold reduction of the probability to obtain a CMR. Also patients homozygous for 3435T and 2677T showed lower probabilities to obtain a MMR and CMR (Table 1). Summarizing, molecular response in CML patients receiving high-dose imatinib strongly depended on SNP-genotype, with the TT-genotype associated with worse response. These findings may be explained by enhanced clearance of imatinib by the 2677TT genotype, which leads to an amino acid substitution and thereby increased transport activity.[4] Enhanced clearance significantly associated with the TT-genotype and less dose reduction was reported earlier by Gurney et al.[5] In addition, recent clinical findings by Ni et al are also in agreement with these results, who studied cytogenetic resistance in patients treated with 400 mg imatinib.[6] These observations are in contrast with the study by Dulucq et al.[1] Strikingly, responses in the French study were strongly related to imatinib plasma levels.[1] Therefore, pharmacokinetic resistance due to a variety of mechanisms affecting plasma levels rather than tumor cell resistance due to P-glycoprotein activity may be suggested as an alternative explanation for these results.

In conclusion, molecular resistance in CML patients receiving high-dose imatinib appeared strongly associated with the TT-genotype of ABCB1, suggesting a role for P-glycoprotein–mediated drug efflux in residual malignant hematopoietic progenitor cells that may possibly account for persistent molecular residual disease.

Table 1. Cumulative incidence of molecular response, by genotype

		Major molecular response (MMR)					Complete molecular response (CMR)				
		At 1 y, %	Univariate		Multivariate†		At 1 y, %	Univariate		Multivariate†	
Allelic variant	No. (%)	(SE)	HR (95% CI)	P*	HR (95% CI)	P*	(SE)	HR (95% CI)	P*	HR (95% CI)	P*
All patients	46	59 (7)					22 (6)				
C1236T, n = 43											
CC	12 (28)	92 (8)	1	.02	1	.03	42 (14)	1	.06	1	.01
CT	23 (53)	52 (10)	.32 (.14-.71)		.31 (.13-.71)		13 (7)	.36 (.16-.82)		.25 (.10-.63)	
TT	8 (19)	50 (18)	.33 (.12-.89)		.40 (.14-1.15)		25 (15)	.48 (.17-1.39)		.27 (.08-.97)	
G2677T, n = 41											
GG	10 (24)	90 (9)	1	.11	1	.21	40 (15)	1	.13	1	.05
GT	23 (56)	61 (10)	.45 (.20-1.05)		.49 (.20-1.16)		22 (9)	.46 (.20-1.08)		.33 (.13-.85)	
TT	8 (20)	38 (17)	.36 (.13-.99)		.42 (.15-1.21)		13 (12)	.35 (.11-1.13)		.23 (.06-.88)	
C3435T, n = 44											
CC	10 (23)	90 (9)	1	.04	1	.06	50 (16)	1	.10	1	.04
CT	24 (55)	58 (10)	.37 (.16-.83)		.35 (.15-.82)		17 (8)	.39 (.17-.92)		.33 (.13-.81)	
TT	10 (23)	40 (15)	.31 (.12-.83)		.35 (.12-.98)		10 (9)	.39 (.13-1.17)		.24 (.07-.83)	

SE indicates standard error; HR, hazard ratio; and CI, confidence interval.

*P values are for the comparison of the molecular response rate between the different allelic variants of each genotype.

†Adjusted for Sokal risk group and cytarabine dose.

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Response

Is there really a relationship between Multidrug Resistance Gene (*MDR1*) polymorphisms and major molecular response to imatinib in chronic myeloid leukemia?

We would like to thank Deenik et al for having given us the opportunity to discuss our results regarding multidrug resistance gene (*MDR1*) polymorphisms and insist on the difficulties associated with the interpretation of single-nucleotide polymorphism (SNP) studies. As cited by Deekik et al, we reported in 2008 the impact of the 3 most relevant polymorphisms of *MDR1* (*ABCB1*) gene on major molecular response (MMR) in 90 CML patients treated for at least 12 months by a standard dose of imatinib (ie, 400 mg) in front-line treatment or in second line after interferon-α.[1] We found a significant difference in genotype frequencies at loci 1236 and 2677 between patients with and those without MMR. In our 2008 report, we concluded that studies in a separate and larger patient population with newly diagnosed CML would be necessary to confirm these preliminary results. In continuation of this, we have now analyzed these 3 SNPs (C1236T, G2677T/A, and C3435T) in 557 of the 636 patients included in the multicenter French SPIRIT trial.[2] Patients were treated de novo by imatinib 400 mg (n = 139), or imatinib 400 mg + Pegylated interferon (IFN) (n = 139), or imatinib 400 mg + cytarabine (AraC) (n = 139), or imatinib 600 mg (n = 140). The proportion of patients in MMR at 12 months was, respectively, 43.9%, 64.7%, 54%, and 55% in the 4 arms. The genotype distributions of each polymorphism were similar to those previously reported, and the 3 variants appeared in partial linkage disequilibrium.[1] A χ^2 test was used to analyze the association between *ABCB1* polymorphisms and MMR within the total cohort and in each arm. For the polymorphism C1236T, no significant difference was observed in genotype frequencies between patients with or without MMR (Table 1). Similarly, no significant difference in genotype frequencies between patients with or without MMR was observed for the G2677T/A polymorphism. However, for the imatinib 400 mg + AraC, the presence of allele G2677 (GA, GG, or GT) was associated with a higher rate of MMR (59.5% vs 32.1%, $P = .009$; not shown in the table). This protective effect of the allele 2677 G in the arm imatinib 400 mg + AraC remained significant after multivariate analysis using a logistic regression model adjusted for Sokal risk, age, and sex (HR = 3.39; 95% confidence interval, 1.37-8.43). This result, which is similar to that found by Deenik et al, is surprising because AraC is not a substrate of MDR1 protein. However, 2 other studies did not identify any association of *ABCB1* gene polymorphisms MMR after imatinib therapy for CML.[3,4]