EUROPEAN
HEMATOLOGY
ASSOCIATION

haematologica

Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

20th Congress of the European Hematology Association
Vienna, Austria, June 11 - 14, 2015

ABSTRACT BOOK

ISSN 0390-6078

Volume 100
JUNE
2015|s1

namely, the frequency of UGT1A1(TA)$_7$ repeat polymorphism is high in Caucasians, whereas it is low in Asians (Beutler *et al. Proc. Natl. Acad. Sci. USA 95 (1998)* 95, 8170–8174).
Aims: The aim of this study was to investigate the association between UGT1A1 gene promoter polymorphism and hyperbilirubinemia in Korean CML patients treated with NIL and RAD as a frontline therapy.
Methods: A total of 94 newly diagnosed chronic phase CML patients who treated with frontline NIL (n=42) and RAD (n=52) was screened for UGT1A1 promoter polymorphism genotype analysis. We used the High Pure PCR Template Preparation Kit (Roche, Germany) to prepare genomic DNA from whole blood and genotyped by direct sequencing of the 253- to 255-bp fragments produced by PCR.
Results: The (TA)$_6$/(TA)$_6$ homozygote and (TA)$_6$/(TA)$_7$ heterozygote were seen in all genotyped population and frequency of (TA)$_6$/(TA)$_6$ homozygote was 77.7% (73/94) in our patients. (TA)$_6$ /(TA)$_6$ homozygote predominated with 78.9% of the alleles in the RAD group and 76.2% in the NIL group. Relative risk for each genotype presented in Table 1, with hyperbilirubinemia defined as CTCAE grade 2 or greater observed at any post-baseline point. The relative risks for 6/6 genotype *versus* 6/7 genotype was 3.9 with 95% CIs of (0.7, 20.3) in the RAD group compared with 10.5 (2.0, 54.3) in the NIL group and NIL group showed significantly high association with UGT1A1 gene promoter polymorphism (P<0.05).

Table 1. Relative risk calculations prevalcence of hyperbilirubinemia.

	Radotinib				Nilotinib		
	Max grade≤1	Max grade≥2	Total		Max grade≤1	Max grade≥2	Total
(TA)6/(TA)6	19	22	41	(TA)6/(TA)6	28	4	32
	46.34%	53.66%			87.50%	12.50%	
(TA)6/(TA)7	2	9	11	(TA)6/(TA)7	4	6	10
	18.18%	81.82%			40.00%	60.00%	
Total	21	31	52	Total	32	10	42
Relative risk=3.9, 95% CI of (0.7, 20.3)				*Relative risk=10.5, 95% CI of (2.0, 54.3)*			

Abbreviation: CI, confidence interval.

Summary and Conclusions: This finding suggests that UGT1A1 gene promoter polymorphism may be an important determinant of hyperbilirubinemia in CML patients with NIL therapy, but not in RAD. However other mechanisms should be explored in patients who have significant hyperbilirubinemia with RAD therapy. Updated data with longer follow-up duration will be presented in the meeting

PB1730

IMPACT OF MULTIDRUG RESISTANCE GENE 1 (MDR1) C3435T POLYMORPHISM ON CHRONIC MYELOID LEUKEMIA RESPONSE TO TYROSINE KINASE INHIBITORS
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Background: Single nucleotide polymorphisms (SNPs) of multiple drug resistance (*MDR1*) gene are associated with altered P-glycoprotein (p-gp) activity and contribute to resistance to tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia (CML).
Aims: We aimed to demonstrate the association between MDR1 gene C3435T polymorphism and molecular response in newly diagnosed chronic phase (CP) CML patients to standard dose upfront imatinib and nilotinib therapy.
Methods: MDR1 C3435T was genotyped using polymerase chain reaction Restriction Fragment Length Polymorphisms (PCR-RFLP) at diagnosis. BCR-ABL1 transcripts level was measured by Real Time Quantitative polymerase chain reaction (RQ-PCR) at diagnosis then every 3 months.
Results: This study included 74 Philadelphia (Ph') positive CP-CML patients; 38 males and 36 females. Median age at diagnosis was 38 years (18-78). Median BCR-ABL1 level was 101%. Forty patients received imatinib (54%) while 34 received nilotinib (46%). Optimal response at 12 month was 35% in the imatinib arm *versus* 80% in the nilotinib arm (P=0.001). The frequency of MDR1 SNP C3435T was 46%, 32% and 22% for CC, TT and CT genotypes, respectively. Optimal response at month 12 differed significantly between imatinib and nilotinib among patients with MDR1 C3435TT genotype (11% *versus* 83%, respectively, P=0.002) while less significant difference was found between the two drugs in CC and CT genotypes (35% vs. 75% and 60% vs. 83%, respectively, P=0.042 & P=0.588).
Summary and Conclusions: MDR1 C3435TT may be used as an additional criterion for initiating nilotinib instead of imatinib as front line therapy for CP-CML patients. We demonstrated the usefulness of MDR1 SNP polymorphism in the identification of CML patients who may or may not respond optimally to imatinib.

PB1731

DIFFERENTIAL EXPRESSION OF ABCF2 IN NEWLY DIAGNOSED AND DASATINIB-TREATED CHRONIC MYELOID LEUKEMIA PATIENTS
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Background: *ABCF2* was previously identified by our group as genes differentially expressed in CML patients which are resistant to imatinib, in samples collected before and after dasatinib treatment (responsive and resistant) in a microarrays analysis study (SILVEIRA, RA *et al. Hematology*;19(1):31-41,2014). *ABCF2* gene is a member of the ATP binding cassette (ABC) transporter family and although its function is not clear, studies with colorectal and breast cancer showed an association of low expression of *ABCF2* and poor prognosis and non-response to palliative chemotherapy. The role of *ABCF2* in CML pathogenesis is unknown.
Aims: The aim of this study was to analyse the expression profile of *ABCF2* in CML patients without previous treatment, in CML patients treated with dasatinib (after imatinib failure) and in healthy donors.
Methods: Total RNA extraction of mononuclear cells from peripheral blood, transcription to cDNA, and qPCR were performed to analyze differential gene expression. *ACTB* and *GAPDH* were used as endogenous control. *geNorm* program was used to estimate the gene expression in arbitrary units (A.U.). Results were expressed as median and compared using non-parametric tests (*Mann Whitney* or *Kruskal-Wallis*). We evaluated 13 healthy donors (control group) and 39 CML patients treated with dasatinib in second line after imatinib failure: 25 responsive to dasatinib, all with complete cytogenetic response (CCyR), 15 of them with major molecular response (MMR) and 14 patients resistant to dasatinib. We also analyzed 9 samples collected at CML diagnosis from the group that was responsive to dasatinib. Only one patient of this group had no sample available after dasatinib treatment.
Results: *ABCF2* expression was down-regulated in the newly diagnosed CML samples and in patients treated with dasatinib compared to control group (0.15 [0.05 – 0.91] *versus* (*vs.*) 0.35 [0.04 – 3.07] *versus* (*vs.*) 2.5 [0.61 – 4.84] P< 0.0001). There was no difference of expression between patients at diagnosis and patients treated with dasatinib (all patients) (*P*=0.09). However, *ABCF2* expression was significantly lower in CML dasatinib-resistant patients when compared to dasatinib-responsive patients with MMR (0.35 [0.05 – 2.21] *versus* (*vs.*) 1.19 [0.14 – 3.07] P=0.02). The expression of *ABCF2* was down-regulated in 8 CML patients at diagnosis and its expression increased after treatment with dasatinib in patients that achieved MMR (0.22 [0.06 – 0.91] *versus* (*vs.*) 1.20 (0.14 – 2.73] P=0.049).

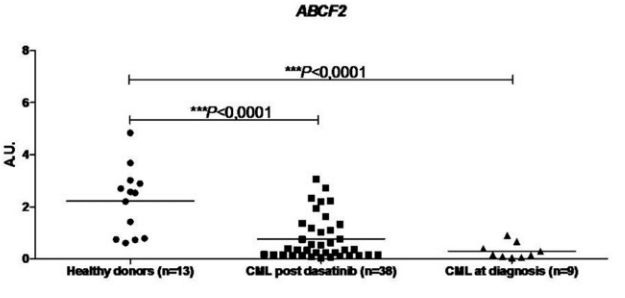

Figure 1.

Summary and Conclusions: *ABCF2* is down-regulated in newly diagnosed CML when compared to the healthy donors and to dasatinib treated patients. On the other hand, up-regulation of *ABCF2* was observed after treatment in patients which achieved MMR with dasatinib. *ABCF2* might be involved in mechanisms associated with the development of CML or resistance. Further studies are necessary to clarify the role of *ABCF2* in CML.

PB1732

DIDO 2 LOW EXPRESSION IN CML IS LINKED TO APOPTOSIS RESISTANCE
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Background: Chronic myeloid leukemia (CML) is a myeloproliferative neo-