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Chronic myeloid leukemia

ABCG2 AND *HAVCR2* SNPS ARE ASSOCIATED WITH LONG-TERM TFR MAINTENANCE IN CML PATIENTS

S. Di Giusto[1], C. Cozzarolo[1], T. Liani[2], M. Moro[2], A. Ermacora[3], R. Stella[4], F. Zaja[4|5] R. Fanin[1|2], D. Damiani[1|2], M. Tiribelli[1|2], E. Toffoletti[1|2]

[1]Division of Hematology and Bone Marrow Transplant, Azienda Sanitaria Universitaria Friuli Centrale; [2]Department of Medicine, University of Udine; [3]Hematology Unit, Azienda Sanitaria Friuli Occidentale; [4]Hematology Unit, Azienda Sanitaria Universitaria Giuliano-Isontina; [5]Department of Medical, Surgical and Health Sciences, University of Trieste.

Background: The new clinical goal for patients with chronic-phase Chronic Myeloid Leukemia (CML) is treatment-free remission (TFR). Currently, no validated predictive biomarker can determine the probability of TFR success. Among the most intriguing are ABC proteins, including ABCG2, membrane transporters implicated in drug resistance, and immune checkpoints, including TIM-3 (encoded by the *HAVCR2* gene), regulators of suppressive pathways.

Aim: To investigate the role of ABC proteins and immune checkpoints genetic polymorphisms in predicting TFR maintenance.

Methods: Among 108 CP-CML patients (median age 66 years, range 29-92), who discontinued TKI therapy (61% imatinib, 26% nilotinib and 13% dasatinib) followed by Hematology Divisions of Udine, Pordenone and Trieste, we analyzed four *ABCB1* (rs1045642, rs2032582, rs1128503, rs3213619), two *ABCG2* (rs2231137 and rs2231142), five *PDCD1* (rs36084323, rs11568821, rs2227981, rs10204525, rs7421861), two *CTLA4* (rs231775 and rs3087243), and two *HAVCR2* (rs1036199 and rs10515746) polymorphisms, as well as the *LAG3* rs870849 polymorphism. We compared TFR rates across different genotypes. Statistical analyses were performed using the Cochran-Armitage trend test under an additive model with the number of minor alleles (0, 1, or 2) as the predictor, survival analysis was conducted using the log-rank (Mantel-Cox) test.

Results: Overall, 68% of patients maintained TFR, whereas 32% resumed TKI therapy after a median of 4 months (range 0–36).

Among the analyzed SNPs, a significant association was observed between the G allele of the *ABCG2* rs2231137 polymorphism and TFR maintenance (12 months TFR maintenance rate: GG=74%, GA=64%, AA=0%, **p=0.027**). Similarly, the minor allele of both *HAVCR2* polymorphisms showed comparable associations: the C allele of rs1036199 (12 months TFR maintenance rate: AA=66%, AC=82%, CC=100%, **p=0.023**), and the A allele of rs10515746 (12 months TFR maintenance rate: CC=65%, CA=83%, AA=100%, **p=0.017**). These results were further supported by log-rank survival analysis based on genotype distribution for TFR maintenance, which confirmed the significance of each variant (**p=0.0038** for *ABCG2* rs2231137, **p=0.038** for the *HAVCR2* rs1036199, and **p=0.025** for *HAVCR2* rs10515746, respectively). Moreover, the two *HAVCR2* SNPs are in linkage disequilibrium.

By combining the two most significant SNPs, a composite score was: +2 points were assigned for each A allele of *ABCG2* rs2231137, and +1 point for each A allele of *HAVCR2* rs10515746. This score demonstrated statistical significance in both logistic regression analysis (**p=0.035**) and log-rank survival analysis (**p=0.0058**) (FIG.1), supporting its potential utility as a predictive marker for TFR outcome.

Conclusions: Despite the relatively small sample size, our findings suggest that *ABCG2* and *HAVCR2* genotypes may influence their respective roles as a drug transporter and immune checkpoint, potentially affecting the ability to maintain TFR after TKI discontinuation.

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