Abstract:

Chronic myeloid leukemia (CML) is a well-treatable disease thanks to targeted therapy with tyrosine kinase inhibitors (TKIs), which in most patients does not result in a shortened lifespan. However, patients are burdened with the lifelong necessity of taking treatment, which is variably toxic. This could be a reason for the inclusion of a new treatment goal in the latest European LeukemiaNet (ELN) recommendations for CML: maintaining treatment-free remission (TFR). To discontinue the treatment, patients must achieve a long-term stable deep molecular response (DMR). Approximately 10-20% of patients are resistant to TKI treatment and do not achieve DMR. One reason for resistance to the most commonly used TKI, imatinib (IM), is its insufficient bioavailability in target cells, caused by changes in the expression and activity of membrane transporters from the ATP Binding Cassette (ABC) and Solute Carrier (SLC) families.

The aim of this study was to find a suitable prognostic marker for achieving an optimal response to IM treatment, which would be available at the time of diagnosis and help in the early identification of patients suitable for a switch to second-generation TKIs, thereby improving their chances of achieving DMR.

Using NGS, we screened SNPs in the promoter regions of 19 genes from the ABC and SLC families and identified SNPs associated with treatment response using Fisher's exact test. These were analyzed in 129 patients in relation to the cumulative achievement of major molecular response (MMR) and event-free survival (EFS). Subsequently, the results were examined in an independent cohort of 269 patients enrolled in TKI discontinuation studies, and their probability of TFR was analyzed.

We identified the SNP rs460089 (promoter of SLC22A4) associated with the response of CML patients treated with IM in the first line. Patients with the rs460089-GC genotype had a higher probability of achieving MMR at 12th month from the start of treatment than patients with the rs460089-GG genotype (P = 0.0001). Patients with the rs460089-GC genotype also had a higher probability of EFS than patients with the rs460089-GG genotype (P = 0.00022). Additionally, we demonstrated that the rs460089 genotype affects TFR in patients enrolled in TKI discontinuation studies. In a cohort of 176 patients from the EURO-SKI study, we showed a higher 6-month probability of survival without molecular relapse in patients with the rs460089-GC genotype (73%, 95% CI: 60-82%) compared to patients with the rs460089-GG genotype (51%, 95% CI: 41-61%). This result was confirmed by analyzing 93 patients from the Polish discontinuation study.

We believe that the screening for the rs460089 genotype will allow identification of patients at high risk of IM treatment failure and could help in deciding on early change of therapy or the suitability of treatment discontinuation upon achieving DMR.

Keywords: chronic myeloid leukemia, imatinib, resistance, SLC transporters, SNP, TFR