LETTER TO THE EDITOR

TPMT status determination: The simplest is the most effective?

Dear Sir,

We carefully read the article by Hindorf and Appell stating that genotyping should be considered the primary choice for pre-treatment evaluation of thiopurine methyltransferase (TPMT) function.1 As evidence since many years, TPMT status should be determined before a thiopurine treatment to identify patients at risk for severe adverse events, as bone marrow suppression, and to propose an individualized dosage.2 Hindorf and Appell mentioned "it is not reasonable to check both genotype and phenotype in all patients." We agree with that statement but we are concerned by the conclusions drawn by the authors and the choice for genotyping as primary choice.1

TPMT genotype is almost exclusively determined on the basis of testing the three mutations 238 G→C, 460 G→A and 719 A→G, defining the most frequent defective TPMT alleles (*2, *3A and *3C), and covering more than 90% of the mutations in the Caucasian population.3 Indeed, as the authors mentioned, assessing only genotype before treatment leads to not detect 8% and 1% of the homozygous and heterozygous mutant patients who are, respectively, at highly and elevated risk of hematological accidents. These patients, at least the homozygous deficient, will develop a potentially lethal hematological adverse event when treated with standard dose of thiopurine while their physician thought to have excluded that risk by a TPMT genotyping.4

Recently, we analyzed the correlation between TPMT phenotype and genotype in 1500 IBD patients from our university hospital.5 Negative predictive value for genotyping to predict a low or intermediate phenotype was 95.3%, meaning that around 5% of the patients with a complete or partial TPMT deficiency will slip through the net. In this situation, we think that phenotype is more powerful to detect patients at risk of hematological adverse event when treated with standard dose of thiopurine while their physician thought to have excluded that risk by a TPMT genotyping.4

Although genotyping is probably the simplest method to identify TPMT deficient patients, phenotyping is more predictive for TPMT activity as it considers genotype, pathophysiological status and environmental factors (e.g. co-prescribed drugs, epigenetic regulation) that can also impact enzyme activity. However, standardization of its determination is challenging, requiring a probable redefinition and refinement of the cut-off values between low, intermediate and rapid TPMT metabolizers.

Conflict of interest

None.

References


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