METABOLISM OF IMUREK
TPMT
(Thiopurine methyltransferase, G460A, A719G and G238C, low metabolizers)

INDICATION

The Thiopurine methyltransferase enzyme (TPMT) catalyzes the methylation of immuno-suppressive medicaments, which are based on the thiopurine, such as the 6-thioguanine, the 6-mercaptopurine or the azathioprine (Imurek). The enzyme activity is characterized by a variable interdividuality and interethnic, which is mainly provoked by some genetic polymorphisms of the gene TPMT. Recently, three main phenotypes of this gene were discovered: rapid, intermediate and slow metabolizers. The consequence of this variability is that patients change their ability to metabolize medicaments (with thiopurine) and secondary effects (low metabolizers) or therapeutic efficiency (rapid metabolizers). The azathioprine is firstly conversed in 6-mercaptopurine, and then a part of it is metabolized in 6-thioguanine (active principle) in an enzymatic process which involved the Hypoxanthine-guanine phosphoribosyltransferase enzymes (HPRT). The rest of the substance is detoxified by the TPMT. People with a low-intermediate TPMT activity (low metabolizers) present some major quantities of the active principle 6-thioguanine. They normally need an inferior dosage of the medicament to gen the therapeutic effect and the suffer from the secondary effects of an extra dosage. In a recent study it was demonstrated a direct correlation between genotype TPMT, the TPMT enzyme activity and the azathioprine answer. This shows that patients with a low activity of TMPT are intolerant to azathioprine.

EPIDEMIOLOGY

About 6-16% of patients have an intermediate activity of the TMPT enzyme. The cause is the heterozygosis (the presence of a polymorphism on a chromosome and the absence on another) and the 0.3% presents with a low or absent enzyme activity (homozygote for one of the polymorphisms). In these cases, if patients receive a standard dosage of thiopurine (for example 75 mg/m2 of corporeal surface per day), they ac cumulate excessive quantities of the thioguanine nucleotide in haematopoietic tissues. This provoke serious and sometimes fatal neuro-suppression. About 20 different mutations were reported, from which 3 are recognized as responsible for a reduced or absent enzymatic activity. Polymorphisms TPMT*3A and TPMT*3C (low metabolizers) are the most common and they gather about the 90% of defective alleles in Europe.

TEST

Highlight of polymorphisms (G460A, A719G and G238C) by means of PCR and restriction analyses. Results are given specifying the allelic form (TPMT*1, *2, *3A, *3B or *3C) with the relative comment regarding the enzymatic activity (low or normal).

SAMPLE TAKING

Blood/EDTA, 5 ml (even a lower quantity in case of difficult sample taking).

EXECUTION

Daily.

Laboratorio di diagnostica molecolare

Further information or bibliographic references can be asked to the laboratory.

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