P4: GENETIC POLYMORPHISM AND THIOPURINE METHYLTRANSFERASE ACTIVITY IN ACUTE LYMPHOBLASTIC LEUKEMIA CHILDREN

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ABSTRACT

Thiopurine methyltransferase (TPMT, E.C.2.1.1.67) is a cytoplasmic enzyme that catalyzes the S-methylation of aromatic and heterocyclic sufhydyl compounds such as anticancer agent, 6-mercaptopurine (6-MP). TPMT activity is regulated by a common genetic polymorphism, associated with large individual variation in thiopurine toxicity and efficacy. The mutant alleles of TPMT have interethnic variability with different frequency and pattern among various ethnic population. The study on the association between genotype and phenotype of TPMT will be of great value in optimizing 6-MP treatment especially in acute lymphoblastic leukemia (ALL) children.

In the present investigation, genetic polymorphism (genotype) and thiopurine methyltransferase activity (phenotype) of TPMT were studied in 90 ALL children. The erythrocyte thiopurine methyltransferase activity was measured by high-performance liquid chromatography (HPLC) technique. The mutant alleles: TPMT*2, TPMT*3A, and TPMT*3C were detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). TPMT activity has shown bimodal frequency distribution with the high and intermediate metabolizers of 93.33% and 6.67%, respectively. There was the correlation between genotype and phenotype of TPMT. 84 ALL children had high TPMT activity (>15 unit/ml of packed RBC/h) with wild type TPMT*1. The other 2 had intermediate activity (5-15 unit/ml of packed RBC/h) with TPMT*1/TPMT*3C. So the mutant allele was found only TPMT*3C. The rest of 4 had unknown genotype with TPMT activity less than 15 unit/ml of packed RBC/h. The possibility for detection of other mutant alleles needs to be considered. Gender had no effect on TPMT activity, however receiving 6-MP affected the activity of TPMT. Therefore phenotype and genotype of TPMT should be performed for minimizing toxicity and maximizing efficacy of 6-MP therapy.

Key words : thiopurine methyltransferase (TPMT), genetic polymorphism, 6-mercaptopurine (6-MP), acute lymphoblastic leukemia (ALL)