Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol10Issue4abst067P.pdf

Inosine Triphosphate Pyrophosphatase Polymorphisms and Mercaptopurine Metabolism in Childhood Acute Lymphoblastic Leukaemia

CS Cartwright[1], C Rowan[1], A Vora[2], L Lennard[1]. [1]Department of Human Metabolism, University of Sheffield, S10 2RX, Sheffield, UK, [2]Department of Haematology, Sheffield Children's Hospital, S10 2TH, Sheffield, UK

Thiopurine methyltransferase (TPMT) regulates the production of cytotoxic thioguanine nucleotide (TGN) metabolites from the thiopurine drug mercaptopurine, a drug widely used in the maintenance chemotherapy of childhood acute lymphoblastic leukaemia (ALL). The TPMT genetic polymorphism is thought to be one of the best textbook examples of clinical pharmacogenetics. TPMT deficiency produces grossly elevated TGN concentrations which precipitates severe, life threatening, bone-marrow toxicity, whereas very high TPMT activity is linked to low TGN concentrations and treatment failure [1]. Thiopurine metabolism is complex and TPMT does not explain all the variation in TGN. A number of enzymes are involved in TGN production; one such enzyme is inosine triphosphate pyrophosphatase (ITPA). *ITPA 94C>A* and *IVS2+21A>C* are SNPs that decrease ITPA activity [2]. The aim of this single centre study was to assess the frequency of *ITPA* mutations in children with ALL and the influence on mercaptopurine metabolism.

A consecutive group of 83 children (53 boys, 30 girls) aged between 1.2 to 15.5 years treated on the ALL2003 protocol were studied. Blood samples were requested at 100% protocol (75mg/sqm), or the maximum tolerated, dose. TGN and methylmercaptopurine nucleotide metabolites (MeMPN; TPMT reaction products) were measured (units; pmol/8x10^8 red cells). Samples were screened for the *TPMT*3* variant family and *ITPA* variants *94C>A* and *IVS2+21A>C*. TGN metabolites ranged from 78 to 1462pmol (median 395) and MeMPNs from 985 to 57048pmol (median 9648); 75 children were *TPMT* wild-type and 8 heterozygous (*TPMT*1/*3A*); 53 children were *ITPA* wild-type, 28 *ITPA* heterozygous (13 for *94C>A* and 15 for *IVS2+21A>C*) and two *ITPA* deficient (one *IVS2+21A>C/IVS2+21A>C* and one compound heterozygote *94C>A/IVS2+21A>C*). *ITPA* allelic frequencies were 0.084 and 0.108 for *94C>A* and *IVS2+21A>C* respectively.

The group was stratified for *TPMT* genotype. Within the *TPMT* wild-type group; 47 children were *ITPA* wild-type, 26 heterozygous (11 *94C>A* and 15 *IVS2+21A>C*) and two *ITPA* deficient. For the two *ITPA* deficient children TGN metabolites were 371 and 581pmols and MeMPN metabolites 9157 and 26488pmols respectively. *ITPA* heterozygous children accumulated significantly lower TGN metabolites, median 270pmol (range 78 to 584) compared to *ITPA* wild-type, median 425pmol (range 150 to 886), median difference 126pmol (95% CI 42 to 205 *P*=0.004). However there was no significant difference for MeMPN metabolites, *ITPA* heterozygous, median 10305pmol (range 1476 to 57048) and *ITPA* wildtype children, median 13398pmol (range 1699 to 46976, *P*=0.769). Only 8 children were *TPMT* heterozygous.

Within the *TPMT* wild-type cohort *ITPA* heterozygous children accumulated significantly lower TGN metabolites than *ITPA* wild-type children. Factors influencing TGN concentrations are of great clinical importance in ALL treatment; children with high TPMT activity and/or those with low TGN metabolites have a higher relapse rate [1,3]. *ITPA* genotyping maybe beneficial in the treatment of ALL.

This work was supported by Leukaemia and Lymphoma Research and a Wellcome Trust summer studentship

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