Thiopurine Methyltransferase Activity In The Clinical Management Of Childhood Acute Lymphoblastic Leukaemia

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The clinical importance of the thiopurine methyltransferase (TPMT) genetic polymorphism has been illustrated by a number of studies which have linked the inheritance of lower TPMT activities with thiopurine sensitivity, specifically bone marrow toxicity. In contrast patients, with very high TPMT may be constitutionally resistant to standard thiopurine doses. We have previously shown that TPMT activity varies between populations of old versus young red cells. When measured at disease diagnosis, TPMT activities in children with acute lymphoblastic leukaemia (ALL) are significantly lower than during chemotherapy [1]. This is attributed to the anaemia of ALL which results in an abnormally old population of circulating red cells, with lower TPMT activities. The aim of this study was to assess the variation in TPMT activity during ALL chemotherapy. The patients studied were treated at the Sheffield Children’s Hospital. Blood samples were obtained at the end of thiopurine containing intensive blocks and during low dose maintenance chemotherapy. During maintenance chemotherapy patients received either thioguanine (TG) or mercaptopurine, MP (standard protocol dose = 100%, 40 or 75mg/m² respectively), the dose was titrated in 25% increments up or down in response to cell counts.

A consecutive group of 130 children (51 girls, 79 boys) aged 1 to 16 years, and diagnosed with ALL between April 1997 and April 2009, were studied; 31 children were randomised to TG and 99 children to MP. The total number of assays was 402; median 4 per child (range 2 to 8). TPMT activities ranged from 4.4 to 26.9 units (intermediate activity <10.5 units; high activity >10.5 units) TPMT activities at adjusted dosages were measured in 43 children; there was no significant difference in TPMT activity measured at 50, 75, 100, 125 or 150% (Kruskal-Wallis, p=0.16). Twenty-three children had TPMT activity measured at the end of a multi-drug intensive block of therapy, at a time when cell counts were low and maintenance therapy had not recommenced, TPMT activity was significantly lower compared to blood samples taken during year 1 maintenance therapy, median difference 5.5 units, p<0.001 (95% CI 4.2 to 6.7) and during year 2 or 3 of maintenance therapy, median difference 1.5 units, p<0.01 (95% CI 0.4 to 2.6). TPMT activity measured during year 1 maintenance therapy, directly after an intensive block, was significantly higher than during year 2 or 3 of maintenance therapy, which contained no intensive blocks of treatment, median difference 2.4 units p<0.001 (95% CI 1.9 to 3.0). However, only 4 children had intra-individual variation in TPMT activity either side of the break point of 10.5 units. There was no significant difference between TPMT activities measured at the beginning of year 2, compared to the end of year 2 or during year 3 of maintenance therapy.

TPMT activity measured under standard conditions, and stable thiopurine dosage, is reproducible. Care should be taken interpreting TPMT activity measurements in children with ALL when blood samples are taken during the 1st year of therapy near multi-drug intensive blocks.

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Reference