Letters to the Editors

Thiopurine methyltransferase measurement may not predict azathiopurine-associated non-myelotoxicity

Sirs,

It is proposed that tolerance to azathiopurine (AZA) can be predicted from laboratory testing. AZA is widely used in the management of autoimmune diseases and as a prodrug requires intracellular conversion to 6-mercaptopurine (6-MP) and subsequent 6-thioguanine nucleotide (6-TGN). The latter binds to DNA with resultant immunosuppressive activity. AZA is alternatively enzymatically metabolised by thio-purine methyltransferase (TPMT) to inactive metabolites 6-methyl-MP or 6-methyl-thioguanine, which shunts the drug away from the 6-TGN activation pathway (1). No or low TPMT activity reportedly predicts increased AZA toxicity. The case presented below raises questions on the clinical value of TPMT monitoring.

A 73-year-old Caucasian man was referred to the Cleveland Clinic for a diagnosis of relapsing polychondritis of three years on long-term prednisone 10 mg daily. Within days after taking AZA 100 mg daily, he developed daily fevers (maximum 102 Fahrenheit) with a normal complete blood cell count (CBC) except for thrombocytopenia of 73,000 (normal 150–400) k/uL. Abnormal serum chemistries included alanine transaminase 80 (normal 5-50) U/L, aspartate aminotransferase 102 (normal 7–40) U/L and total protein 4.8 (normal 6–8.4) g/dl. Alkaline phosphatase, total bilirubin, creatinine kinase and sedimentation rate were normal. There was a new onset of proteinuria 300 mg/dl, haematuria and elevated serum creatinine of 1.4 (normal 0.7–1.40) mg/dl. AZA was discontinued after 8 weeks due to a concern for drug toxicity when his creatinine was 5.1 mg/dl, blood urea nitrogen 59 (normal 10–25) mg/dl and potassium 5.6 (normal 3.5–5.0) mmol/L. He promptly became afebrile, the serum creatinine decreased to 1.94 mg/dl, and chemistries normalised approximately 10 days after discontinuation AZA. Three weeks later, repeat CBC and creatinine normalised with a mild anaemia. The following were negative or normal: antinuclear, anti-extractable nuclear antigens, ant-dsDNA and anti-neutrophil cytoplasmic autoantibodies, complements 3 and 4, serum thyroid-stimulating hormone and hepatitis panel. Physical examination was normal except for "floppy ears".

AZA is associated with adverse events in 37% of patients such as myelosuppression (3%), hepatotoxicity, pancreatitis, rash and fever (2). Our patient developed fever, thrombocytopenia, elevated liver enzymes, proteinuria, haematuria and subsequent acute renal failure while taking AZA, which normalised after discontinuation, suggesting development of AZA related toxicity. Of note, the AZA renal toxicity is rare with only a single case report that AZA induced acute interstitial nephritis as the cause of rapidly progressive renal failure in a patient with Wegener's granulomatosis (3).

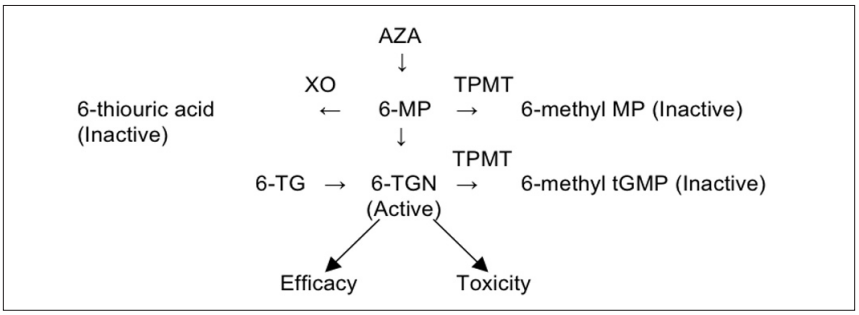

Fig. 1. Diagnostic flow chart for the detection of impaired azathiopurine metabolism.
AZA: azathiopurine; 6-MP: mercaptopurine; TPMT: thiopurine S-methyltransferase; XO: xanthine oxidase; 6-TG: thioguanine; 6-TGN: thioguanine nucleotide. AZA, 6-MP and 6-TG are enzymetically metabolized to active 6-TGN which both exerts efficacy and causes toxicity. Measurement of TPMT, 6-MP and 6-TGN is clinically used to monitor AZA toxicity which is also checked by regular measurement of complete blood count and comprehensive metabolic panel.

TPMT testing includes enzyme level testing (phenotypic testing) and DNA based testing (genotypic testing) by polymerase chain reactions (1). Phenotype testing involves the conversion of 6-MP to radiolabeled 6-methyl MP in erythrocyte lysate, thus can be affected by blood transfusions. TPMT activity may be induced by AZA and 6-MP but inhibited by sulfasalazine and 5-acetylsalicylic acid (4). Approximately 90% of the population are homozygous for a high-activity TPMT allele (wild-type), and the remaining are homozygous for a low-activity allele and heterozygous. The wild-type allele is defined as TPMT*1 and the most commonly detected low-activity alleles are TPMT*3A (G460A and A719G) and TPMT*3C (A719G) (5). It is reported that TPMT genotype testing is a more rapid method of identifying patients at risk for acute toxicity from AZA in rheumatic disease (6). Identification of TPMT polymorphisms may not predict myelosuppression in systemic lupus erythematosus (7). Both phenotype and genotype testing was normal in our case suggesting that TPMT testing alone is not sufficient to adequately personalise the AZA dosage in rheumatic patients (8), although a single case report has its limitation. TPMT measurement can predict myelotoxicity but appears to explain less than 30% of the cases of myelosuppression on AZA or 6MP treatment. Moreover, AZA toxicity other than myelosuppression can not be predicted by TPMT testing (9). As shown in Figure 1, measurement of TPMT, 6MP and 6-TGN may be clinically employed to monitor AZA toxicity. It is generally recommended that a slow escalation of AZA dosage at initiation of the medication should be followed and AZA is best avoided in homozygous TPMT mutants (10).

In conclusion, TPMT testing is one of the several modalities used to monitor AZA related myelosuppression but is unable to predict other adverse events such as hepatic and renal toxicity. Therefore, routine tests such as CBC and metabolic panel remain the mainstay of the surveillance of all potential adverse reactions.

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