Fatal azathioprine toxicity in a patient with low thiopurine methyltransferase (TPMT) activity

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Background

We report a fatal case of azathioprine-induced bone marrow failure in a patient with low thiopurine methyltransferase (TPMT) activity. TPMT is one of the enzymes involved in azathioprine metabolism. Reduced enzyme activity is associated with azathioprine myelotoxicity. Activity can be estimated by TPMT genotyping.

Clinical features

The patient was a 59 year old female who had a renal transplant in early 2015. Her initial immunosuppression regimen was mycophenolate mofetil, prednisolone and tacrolimus.

Post-transplant recovery was complicated by chronic diarrhoea. The patient was transitioned from mycophenolate mofetil to mycophenolate sodium and the dose reduced.

In January 2016 the patient travelled to a Pacific island. While overseas on holiday, her diarrhoea worsened, requiring hospitalisation. Mycophenolate was ceased and azathioprine commenced. TPMT activity had not been quantified at this time.

She returned to Australia two weeks later but was troubled with persistent diarrhoea and a productive cough. One month after starting azathioprine, severe pancytopenia was noted and the patient was admitted to hospital. Azathioprine was ceased on admission. Pancytopenia persisted despite three weeks of treatment with filgrastim and blood products; complications included febrile neutropenia and polymicrobial sepsis. The patient continued to deteriorate.

It was subsequently found that the patient had a low TPMT genotype, which resulted in her being extremely sensitive to the myelosuppressive effects of azathioprine. She died one month after admission. The cause of death was multi-organ failure secondary to bone marrow failure.

Metabolism of Azathioprine

Low TPMT activity increases production of the myelosuppressive 6-TGN metabolite (bolded arrows)

Discussion

Approximately 11% of the population has moderately reduced TPMT activity, while only 0.3% has severely reduced TPMT activity [1,2]. In these patients active 6-mercaptopurine accumulates, leaving a larger proportion to be converted to cytotoxic 6-thioguanine nucleotide analogues. This can lead to bone marrow toxicity and myelosuppression.

TPMT genotyping is possible but it can take up to four weeks at our centre for results to become available to the treating clinician.

This case has been presented at the hospital Adverse Drug Reaction and Drugs and Therapeutics Committees. Discussion has highlighted that TPMT testing might be an under-utilised pre-screening tool. In the inpatient setting, neutropenia can be detected early and therapy modified. Unfortunately for our patient, azathioprine was started overseas in the setting of acute illness. Close monitoring was difficult and TPMT genotype not performed. This is pertinent as azathioprine is commonly prescribed in the outpatient setting for autoimmune conditions and its use can often be anticipated.

Conclusion

This case highlights that low TPMT activity, although an uncommon finding, can have dire consequences, particularly where intensive monitoring is not practical.

We would like to acknowledge the patient’s family for permitting use of this case for our report.