COMPARISON BETWEEN THE MAXIMUM RECOMMENDED DOSE OF AZATHIOPRINE ACCORDING TO THE ENZYMATIC ACTIVITY OF THIOPURINE METHYLTRANSFERASE AND 6-THIOGUANINE LEVELS WITH THE MAXIMUM TOLERATED DOSE

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Background and importance

Azathioprine (AZA) is an analog of purines used in the inflammatory bowel disease (IBD) treatment. AZA is transformed by thiopurine methyltransferase (TPMT) into its metabolites; 6-methylmercaptopurine (6-MMP) and 6-thioguanine (6-TGN).

Aim and Objectives

1. Analyze the prevalence of deficient, low, intermediate, moderate and high TPMT activity.
2. Evaluate the MTD and 6-TGN levels.
3. Compare the maximum recommended dose of AZA according to thiopurine methyltransferase (TPMT) activity and the maximum tolerated dose (MTD).

Results

131 patients, 61 (46.6%) women, mean age 34.7 (17.4) years.

When analyzing the dosage according to the TPMT activity and MTD, it was observed that according MTD, it was:
- Higher in 30 (22.9%) patients.
- Within the range in 58 (44.3%) patients.
- Lower in 43 (32.8%) patients.

Recommended 6-TGN levels (target 300-550 pmol/0.2 ml) in the patients receiving the MTD were:
- Higher in 35 (26.7%) patients.
- Within the range in 72 (54.9%) patients.
- Lower in 24 (18.3%) patients.

Patients with 6-TGN levels <300 pmol/0.2 ml:
Median 6-MMP/6-TGN ratio: 1.5.
3 (2.3%) patients had a 6-MMP/6-TGN ratio >4.

Mean serum creatinine: 0.70 (0.35) mg/dl.
Patients’ renal function did not influence in the elimination of AZA metabolites.

Conclusion and Relevance

The phenotypes of intermediate and moderate activity of TPMT were the most prevalent. 6-TGN levels were high in some patients increasing the risk of toxicity. In most patients, the recommended dose based on TPMT activity was not coincident with MTD, suggesting the need to detect other genetic factors that might influence AZA metabolism.

Material and methods

Retrospective observational study
- From February 2017 to May 2021

Patients with IBD treated with AZA with a determination of enzymatic activity of TPMT

Demographic, clinical data, 6-TGN levels and phenotype [activity of TPMT (IU/ml), determined by HPLC] were collected.

AZA dosage according to TPMT activity following the Vall d’Hebron Hospital protocol
- Poor activity; TPMT<5.0 U/mL RBC: AZA not recommended
- Low activity; TPMT 5.1-13.7 UI/ml: AZA 0.5 mg/kg
- Intermediate activity; TPMT 13.8-18 UI/ml: AZA 1.5 mg/kg
- Moderate activity; TPMT 18.1-26.0 UI/ml: AZA 2.5 mg/kg
- High activity; TPMT 26.1-40.0 UI/ml: AZA 3.0 mg/kg.

No patients with poor or high TPMT activity were detected in the study population.

The AZA posology was:
- Decreased in 31 (23.7%) patients.
- Withdrawn in 22 (16.8%) due to adverse events.

Most frequently adverse events detected were:
- Digestive intolerance: 10 (7.6%) patients.
- Leukopenia: 7 (5.3%) patients.
- Lymphopenia: 5 (3.8%) patients.
- Hypertransaminasemia: 4 (3.1%) patients.
- Nausea: 3 (2.3%) patients.

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