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Meeting abstract

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Pharmacogenetics of thiopurine therapy: from thiopurine S-methyltransferase to S-adenosylmethionine

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Background

The efficiency and safety of the thiopurine therapy rely on the concentration of patient's cytotoxic thioguanine nucleotides (TGN), which in turn depend on the deactivation of thiopurine drugs by thiopurine S-methyltransferase (TPMT). The activity of TPMT largely depends on the presence of genetic polymorphisms. Determination of mutations in the TPMT gene before starting 6-mercaptopurine (6-MP) therapy represents a quick, simple and cost-effective strategy to individualize thiopurine dosing. However, TPMT phenotype-to-genotype correlation is not complete, indicating a need for identification of novel biomarkers. The prime candidate is S-adenosylmethionine (SAM) which by binding into the active site of TPMT stabilizes its structure and consequently influences the metabolism and toxicity of thiopurine drugs [1].

Methods

6-MP-induced cytotoxicity was studied in MOLT cells. Metabolic activity of cells was determined by the CellTiter Aqueous One Proliferation Assay. Cytosolic TGN, SAM and methylthioinosine monophosphate (MeTIMP) levels as well as TPMT activity were measured by the modified reverse-phase HPLC method. Intracellular ATP levels were determined by the CellTiter Glo Luminescent Cell Viability Assay (Promega). Apoptotic cells were detected by the Annexin V-FITC Apoptosis Detection Kit (Sigma) and visualized by fluorescence microscopy. Caspase-3 activity was measured using labeled DEVD substrate.

Results

We herein present evidence of a novel TPMT-mediated mechanism of SAM-specific effects on 6-MP-induced cytotoxicity [2]. Our results show that exogenous SAM rescues cells from the toxic effects of 6-MP by restoring cell proliferation and delaying the onset of apoptosis. This is achieved by altering the dynamics of 6-MP metabolism, resulting in lower production of TGNs and MeTIMP. We prove that the extent of MeTIMP-induced inhibition of *de novo* purine synthesis (DNPS) determines the concentrations of intracellular ATP, and consequently SAM, which acts as a positive modulator of TPMT activity. This leads to a greater conversion of 6-MP to inactive 6-methylmercaptopurine, and lower availability of thioinosine monophosphate for the biotransformation to TGNs and MeTIMP. By acting as a TPMT-stabilizing factor, the availability of SAM contributes to the extent of 6-MP cytotoxicity.

Conclusion

By identifying SAM as an important modulator of TPMT activity and consequently thiopurine toxicity, novel rationalization of the therapy may apply.

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