Glutathione S-Transferase M1 polymorphism – A risk factor for hepatic venoocclusive disease in bone marrow transplantation.

The frequencies of GST MI and GST TI null genotypes were similar compared to that of the healthy controls and also to that reported for Asian population.

COMMENTS

Hepatic veno occlusive disease (HVOD) is an important complication of bone marrow transplantation. The reported incidence of this complication varies between 10 and 20%,1-3 and in thalassemic patients with pre-existing hepatic dysfunction can be as high as 45%. The pathogenesis of HVOD is not fully understood but it is considered to occur due to the damage to the sinusoidal endothelial cells (SEC) and the surrounding centrilocular hepatocytes, usually mediated by the conditioning regimen. The enzyme glutathione S-transferase is responsible for the hepatic metabolism of both busulfan and cyclophosphamide.

Busulfan is metabolized by GST to form positively charged sulfonium ion which is cleaved to a lipophilic compound tetrahydrothiophene which is toxic to SEC and hepatocytes. As busulfan is given before cyclophosphamide, the metabolism of busulfan is responsible for depletion of hepatic cytosolic glutathione which is necessary for detoxification of cyclophosphamide. This can lead to cyclophosphamide mediated hepatic injury.4

This study establishes GST MI null genotype as a definite risk factor for HVOD. There are 2 possible explanations for this. One is that, absence of GST MI isoform increases the level of GSTAI isoform which is the most active isoform of the enzyme.5,6 This can lead to increased production of the toxic busulfan metabolite and greater depletion of cytosolic glutathione. The other hypothesis is that GSTMI genotype codes for an enzyme that could be protective to the SEC / hepatocytes. The clearance of busulfan is higher and the steady state concentration lower in those with GST MI null genotype establishing the fact that busulfan metabolism is accelerated in this genotype. The pre BMT hepatic glutathione-level did not show any correlation with HVOD as glutathione depletion occurs only after exposure to the drugs. Hence a hepatic glutathione level post conditioning in all patients and its correlation with HVOD would have been ideal.

The importance of this study lies in its potential for therapeutic application. Prospective bone marrow transplant patients who are positive for GST MI null genotype should have their conditioning regimen modified in order to prevent this serious and sometimes fatal complication.

REFERENCES:


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