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721.ALLOGENEIC TRANSPLANTATION: CONDITIONING REGIMENS, ENGRAFTMENT AND ACUTE TOXICITIES

The Influence of Methotrexate-Related Transporter and Metabolizing Enzyme Gene Polymorphisms on Peri-Engraftment Syndrome and Graft-Versus-Host Disease after Haplo-Hematopoietic Stem Cell Transplantation in Pediatric Patients with Malignant Hematological Diseases

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Background: Methotrexate (MTX), utilized as a graft-versus-host disease (GvHD) prophylactic agent in allogeneic hematopoietic stem cell transplantation (allo-HSCT), has been proven to effectively decrease the occurrence of the peri-engraftment syndrome (Peri-ES) and acute GvHD (aGvHD). Changes in the pharmacodynamics of MTX are closely associated with gene polymorphisms in genes encoding drug-metabolizing enzymes and transporters. Nevertheless, the current studies mainly concentrate on leukemia or autoimmune diseases, and limited studies on the allo-HSCT were reported.
Methods: Here, we retrospectively assessed the relationship between MTX-related transporter and metabolizing enzyme gene polymorphisms, clinical characteristics and outcomes in 57 pediatric patients, who received haploid HSCT (haplo-HSCT), with malignant tumors at a single center. Log-rank test and Cox proportional regression model were used for univariate and multivariate analysis, respectively. A significance level of 0.05 was used for all analyses.
Results: At baseline, the mean age at HSCT was 5.1 years old, and more males (80.8%) were enrolled in our cohort. Acute leukemias, including mixed phenotype acute leukemia (MAPL), was the most common etiology, which constituted 94.7% (54/57) of the cohort. All patients achieved hematopoietic recovery from haploidentical donors. The median time to neutrophil and platelet engraftment was 12 days (range, 10-23), 12 days (range, 5-39), respectively. A total of nine kinds of gene polymorphisms were detected and the most common variant type was ABCB1 (1236C>T), followed by MTHFR (665C>T) and ABCB1 (3435C>T). All gene polymorphisms were in Hardy-Weinberg equilibrium in our cohort. We observed the median platelet recovery time of 16 days (range, 10-24 days) for ABCB1 (1236C>T) CC genotype was significantly longer than the median time of 11.5 days (range, 5-39 days) for TC/TT genotype (P = 0.042). In this study, 61.4% of patients (35/57) developed Peri-ES, and 36.8% patients (21/57) developed grade II-IV aGvHD, including 8 (14.0%) with grade II, 8 (19.3%) with grade III, and 5 (8.8%) with grade IV. Compared with SLCO1B1 (1865+4846T>C) TT, patients with SLCO1B1 (1865+4846T>C) TC/CC had the increased incidence of Peri-ES (75.9% vs 46.4%, P = 0.030). Based on the multivariate Cox analysis, we discovered that SLCO1B1 (1865+4846T>C) TT genotype was an independent protective factor for Peri-ES morbidity (hazard ratio (HR)= 0.464; 95% confidence interval (CI)=0.231-0.931; P=0.031). Additionally, when compared with mononuclear cells (MNC) low dose according to the median dose value (cutoff: 6.99×10^{8}/kg) in our cohort, patients with MNC high dose had the increased incidence of II-IV aGvHD (50.0% vs 24.1%, P = 0.030). Cox regression analysis identified that the dose of MNC reinfused was significantly related with II-IV aGvHD as an independent risk factor in multivariate analysis (HR = 2.604; 95% CI=1.049-6.463; P = 0.039). Unfortunately, no differences was discovered between aGvHD after haplo-HSCT and MTX-related gene polymorphisms.
Conclusion: In summary, our findings prove that the host's genotypes might modify the risk of developing Peri-ES, contribute to a better understanding of the inter-individual difference in efficacy, and facilitate the development of individualized approaches to GvHD prophylaxis.

Disclosures No relevant conflicts of interest to declare.

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