Association of Busulfan Exposure and Outcomes after Hematopoietic Cell Transplantation for Patients with an Inborn Error of Immunity

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Background

Allogeneic hematopoietic cell transplant (HCT) is a potentially curative treatment strategy for patients with inborn errors of immunities (IEIs). The objective of this study was to assess the optimal busulfan exposure prior to allogeneic HCT for patients with an IEI who received an intravenous busulfan-based conditioning regimen between 2000 and 2023.

Methods

Patients from 17 international centers were included. Main outcome of interest was event-free survival (EFS). Patients were categorized into 4 IEI subgroups: combined immunodeficiency (CID), severe combined immunodeficiency (SCID), neutrophil disorders and hemophagocytic lymphohistiocytosis (HLH)-related disorders. Busulfan exposure was calculated by individual centers (AUC_{CENTER}) and was re-estimated using a validated pharmacokinetic model (AUC_{NONMEM}).

Results

Overall, 562 patients were included: 173 (30.8%) CID, 154 (27.4%) SCID, 101 (18.0%) HLH-related disorders, and 134 (23.8%) neutrophil disorders. Median busulfan AUC_{NONMEM} was 69.0 mg×h/L and correlated poorly with AUC_{CENTER} (r^2=0.54). Patients with SCID, HLH-related, and neutrophil disorders were analyzed together

(n=389), because CID disease subtype was an effect modifier (p=0.03). Estimated 2-year EFS was 78.5%. In patients with the found optimal busulfan AUC_{NONMEM} of 70-90 mg×h/L, 2-year EFS was superior to <70 mg×h/L (adj-HR 1.97, 95% CI 1.11-3.49, p=0.02), and >90 mg×h/L (adj-HR 5.05, 95% CI 2.43-10.49, p<0.0001). Full donor chimerism increased with higher busulfan AUC_{NONMEM}, plateauing at 90 mg×h/L. For CID patients, optimal AUC_{NONMEM} for donor chimerism was found to be >70 mg×h/L.

Conclusion

Improved EFS and higher donor chimerism may be achieved by targeting a cumulative busulfan AUC_{NONMEM} of 80 mg×h/L (range 70-90). Our study stresses the importance to uniformly using a validated population PK-model to estimate the AUC_{NONMEM}.