

Center for Stem Cell Biology and Regenerative Medicine

Division of Stem Cell Transplantation

幹細胞移植分野

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We are studying the clinical promotion and medical development of hematopoietic stem cell transplantation with a focus on cord blood transplantation. We conducted 23 allogeneic transplantation in 2024 in the Department of Hematology & Oncology. In addition to data on hematopoietic stem cell transplantation, we are analyzing various issues related to clinical transplantation using the Japanese transplant database. Basic studies include the development of efficient in vitro amplification of patient-derived primary cells and preclinical studies on the use of virus-specific CTLs in post-transplant and other immunocompromised patients. Our goal is to make allogeneic transplantation a safer treatment option and extend it to older patients.

1 Levels of C-Reactive Protein and Body Temperature Elevation During Neutropenia Predict Engraftment and Non-Relapse Mortality for Unrelated Single-Unit Cord Blood Transplantation in Adults.

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Cord blood transplantation (CBT) presents unique challenges related to inflammation during neutropenia, such as mucosal damage, infections, and the potential development of pre-engraftment syndrome or pre-engraftment immune reaction. These factors can contribute to significant inflammation and infection shortly after CBT. However, the effect of severe inflammation during neutropenia, specifically elevated C-reactive protein (CRP) level and body temperature, on post-transplant outcomes after CBT remains un-

clear. This retrospective study aimed to investigate the association between maximum CRP level, maximum body temperature during neutropenia, and post-transplantation outcomes in adult patients undergoing single-unit CBT. We retrospectively evaluated the impact of maximum CRP level and maximum body temperature during neutropenia on post-transplantation outcomes in adults who underwent single-unit unrelated CBT between 1998 and 2023 at our institution. A total of 336 adult patients were included in this study. The median maximum CRP level before neutrophil recovery was 7.75 mg/dL (interquartile range [IQR], 4.70 to 12.05 mg/dL) at a median of 14 d (IQR, 8 to 16 d). The median maximum body temperature before neutrophil recovery was 39.5°C (IQR, 39.0 to 40.0°C) at a median of 15 d (IQR, 12 to 17 d). In the multivariate analysis, a maximum CRP level ≥ 20 mg/dL was significantly associated with lower neutrophil recovery (hazard ratio [HR], 0.37; 95% confidence interval [CI], 0.23 to 0.59; $P < .001$), lower platelet recovery (HR, 0.28; 95% CI, 0.16 to 0.48; $P < .001$), and a higher incidence of veno-occlusive disease/sinusoidal obstruction syndrome (HR, 16.42; 95% CI, 4.11 to 65.54; $P < .001$), which resulted in higher non-relapse mortality (NRM) (HR, 5.16; 95% CI, 2.62 to 10.15; $P < .001$) and worse overall survival (HR,

2.81; 95% CI, 1.66 to 4.78; $P < .001$). Similarly, a maximum body temperature $\geq 40.5^{\circ}\text{C}$ was significantly associated with lower neutrophil recovery (HR, 0.51; 95% CI, 0.33 to 0.79; $P = .002$), lower platelet recovery (HR, 0.55; 95% CI, 0.38 to 0.79; $P = .001$), higher incidence of grades III to IV acute GVHD (HR, 2.93; 95% CI, 1.24 to 6.88; $P = .013$), and extensive chronic GVHD (HR, 2.47; 95% CI, 1.22 to 4.97; $P = .011$), which resulted in higher NRM (HR, 3.43; 95% CI, 1.53 to 7.67; $P = .002$). Maximum CRP level and maximum body temperature during neutropenia were significantly associated with lower hematopoietic recovery and higher NRM following single-unit CBT in adults. Further studies are warranted to explore early intervention strategies aimed at preventing severe inflammation and improving post-transplant outcomes in single-unit CBT.

2 Feasibility and safety of the discontinuation of systemic immunosuppressive treatment after single-unit cord blood transplantation in adults.

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We retrospectively evaluated the incidence, factors, and clinical outcomes of the discontinuation of immunosuppressive treatment (IST) after single-unit unrelated cord blood transplantation (CBT) in adults receiving cyclosporine-based graft-versus-host disease (GVHD) prophylaxis at our institute. Among the 309 patients who achieved engraftment, 247 were able to discontinue IST with a median follow-up of 121 months for survivors. The cumulative incidence of the discontinuation of IST was 46.2% at 180 days, 72.8% at 2 years, and 79.3% at 5 years post-CBT. In the multivariate analysis, discontinuation of IST after CBT was significantly associated with the requirement for steroid therapy (hazard ratio [HR]: 0.46; $P < 0.001$) and the recent calendar year of CBT (HR: 1.79; $P < 0.001$). In the conditional landmark analysis at 180 days, discontinuation of IST was not associated with the development of extensive chronic GVHD (HR: 1.00; $P = 0.989$), non-relapse mortality (HR: 0.49; $P = 0.122$), relapse (HR: 1.46; $P = 0.388$), or overall survival (HR: 1.91; $P = 0.065$). Our data showed that successful discontinuation of IST is common after single-unit CBT in adults. Discontinuation of IST did not affect subsequent outcomes, suggesting that discontinuation of IST is both feasible and safe in adults undergoing single-unit CBT.

3 Association of individual comorbidities with outcomes in allogeneic hematopoietic cell transplantation from unrelated adult donors versus unrelated cord blood: A study on behalf of the Donor/Source and Transplant Complications Working Groups of the Japanese Society for Transplantation and Cellular Therapy.

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We retrospectively evaluated the effect of 17 individual comorbidities, defined by the hematopoietic cell transplantation (HCT)-specific comorbidity index, on non-relapse mortality (NRM) and overall survival (OS) in 9531 patients aged between 16 and 70 years who underwent their first allogeneic HCT from 8/8 and 7/8 allele-matched unrelated donors (8/8 and 7/8 MUDs) or single-unit unrelated cord blood (UCB) between 2011 and 2020 using data from a Japanese registry database. In the multivariate analysis, infection (adjusted hazard ratio [HR], 1.62, 95% confidence interval [CI], 1.33-1.99 for 8/8 and 7/8 MUDs; adjusted HR, 1.33, 95%CI, 1.12-1.58 for UCB) and moderate/severe hepatic comorbidity (adjusted HR, 1.57, 95%CI, 1.04-2.38 for 8/8 and 7/8 MUDs; adjusted HR, 1.53, 95%CI, 1.09-2.15 for UCB) had a significant impact on NRM in both donor groups. Cardiac comorbidity (adjusted HR, 1.40, 95%CI, 1.08-1.80), mild hepatic comorbidity (adjusted HR, 1.22, 95%CI, 1.01-1.48), rheumatologic comorbidity (adjusted HR, 1.67, 95%CI, 1.11-2.51), renal comorbidity (adjusted HR, 2.44, 95%CI, 1.46-4.09), and severe pulmonary comorbidity (adjusted HR, 1.40, 95%CI, 1.11-1.77) were significantly associated with an increased risk of NRM but only in UCB recipients. Renal comorbidity had the strongest impact on poor OS in both donor groups (adjusted HR, 1.73, 95%CI, 1.10-2.72 for 8/8 and 7/8 MUDs; adjusted HR, 2.24, 95%CI, 1.54-3.24 for UCB). Therefore, unrelated donor selection should be taken into consideration along with the presence of specific comorbidities, such as cardiac, rheumatologic, renal, mild hepatic, and severe pulmonary comorbidities.

4 Development of ex vivo amplification system for patient-derived hematopoietic malignant cells

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We have developed an optimized serum-free and OP9-free culture system for primary tumor specimens (PTS) from AML patients, focusing on the long-term maintenance and expansion of CD45 dim CD34+ leukemia stem-like cells. By reducing cytokine complexity, incorporating serum substitutes such as Soluplus, and introducing small molecules including Pomalidomide, UM729, and SR-1, we achieved significant improvements in PTS culture efficiency. Our system supports the long-term expansion of leukemia stem-like cells while maintaining their functional properties, as demonstrated by clonogenic assays and CRISPR-Cas9 gene-editing experiments.

This optimized culture system provides a promising alternative to traditional serum- or feeder-dependent methods, offering a robust platform for leukemia research and therapeutic development. The ability to expand PTS *ex vivo* opens new opportunities for studying leukemia stem cell biology, drug resistance mechanisms, and personalized medicine approaches.

Publications

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