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. In addition to data on hematopoietic stem cell transplantation, we are analyzing various issues related to clinical transplantation using the Japanese transplant database. Our goal is to make allogeneic transplantation a safer treatment option and extend it to older patients.

1. Assessment of cellular and humoral immunity against varicella-zoster virus in adult allogeneic hematopoietic cell transplant recipients: a cross-sectional study assessing cellular immunity after administration of an adjuvanted recombinant zoster vaccine.

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Allogeneic hematopoietic cell transplantation (HCT) recipients have a high risk of developing the reactivation of latent varicella-zoster virus (VZV), which is partly due to an attenuated cellular immunity. Recently, the adjuvanted recombinant zoster vaccine (RZV) has been demonstrated to be safe in allogeneic HCT recipients. However, evaluations of cellular and humoral immune responses to vaccination and reactivation in these populations remain limited. We performed a cross-sectional, comprehensive analysis of cellular immunity using a dual-color enzyme-linked immunosorbent spot (ELISpot) assay capable of detecting both interferon-gamma (IFN-γ) and interleukin-2 (IL-2)-secreting T cells in response to VZV glycoprotein E (gE) antigens in 44 allogeneic HCT recipients. The median interval from HCT to sample collection was 43 months (range, 9-220 months). Prior to sample collection, 16 patients received the RZV, whereas 20 patients experienced zoster reactivation after allogeneic HCT. The median anti-VZV IgG antibody level was 347.5 mIU/mL (range, 50-13,650 mIU/mL). ELISpot assays revealed that gE-specific IFN-γ- and IL-2-producing T cells were present in 60.0 % and 18.2 % of patients, respectively. Antibody levels did not correlate with the frequency of IFN-γ-producing T cells (r = 0.152, P = 0.324) or IL-2-producing T cells (r = 0.216, P = 0.157). Patients who experienced zoster reactivation and received vaccination had higher antibody levels and more frequent gE-specific IFN-γ-producing T cells compared to those without either. Both zoster reactivation and vaccination were associated with enhanced cellular

and humoral immunity against VZV in adult allogeneic HCT recipients.

2. Has early mortality following single-unit unrelated cord blood transplantation improved in recent years? A nationwide registry data analysis from 2003 to 2022 in Japan.

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Unrelated single-unit cord blood transplantation (CBT) is a valuable alternative donor source for patients without matched related or unrelated donors. Although initial concerns included limited cell dose, delayed haematopoietic recovery and higher early mortality, advancements in transplant practices may have led to improved outcomes. However, it remains uncertain whether these improvements extend to the most recent years. We conducted a nationwide, registry-based retrospective study of 15 816 patients who received unrelated single-unit CBT in Japan and analysed across four time periods: 2003-2007, 2008-2012, 2013-2017 and 2018-2022. Overall survival (OS) improved significantly across time periods, with 3-year OS increasing from 38.8% (2003-2007) to 54.4% (2018-2022; $p < 0.001$). Similarly, 100-day non-relapse mortality declined from 19.6% to 9.5% ($p < 0.001$). Neutrophil and platelet engraftment rates also rose steadily, reaching 89.6% and 78.0%, respectively, in the most recent period. The most notable improvement in 100-day OS occurred among patients aged ≥60 years. Early mortality within 100 days due to bacterial and fungal infections, graft failure, haemorrhage and graft-versus-host disease (GVHD) significantly decreased over time. This study shows clear and consistent improvements in transplant outcomes, especially in the most recent 5-year period.

3. Prognostic factors for allogeneic haematopoietic cell transplantation outcomes in primary refractory acute myeloid leukaemia (2013-2022): A retrospective study by the adult acute myeloid leukaemia working group of the Japanese Society for Transplantation and Cellular Therapy.

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Primary refractory acute myeloid leukaemia (AML) remains a major clinical challenge, with poor outcomes despite salvage chemotherapy. Allogeneic haematopoietic cell transplantation (HCT) continues to be a potentially curative option for these patients. However, recent data on outcomes and prognostic factors specific to primary refractory AML remain limited. We conducted a retrospective analysis of 2600 adult patients with primary refractory AML who underwent their first allogeneic HCT between 2013 and 2022, using data from the Japanese national registry. The 3-year overall survival (OS) and leukaemia-free survival (LFS) rates were 28.5% and 24.4% respectively. The multivariate analysis identified older age (≥50 years), poor performance status (≥2), adverse cytogenetics, extramedullary disease at diagnosis and higher peripheral blood blast count at HCT (≥10%) as significant risk factors for worse OS and LFS. The cumulative incidences of relapse and non-relapse mortality at 3 years were 49.8% and 25.8% respectively. Based on the five significant risk factors, we developed a scoring system that effectively stratified patients into distinct prognostic groups for OS and LFS. This nationwide analysis demonstrated that allogeneic HCT offers the potential for long-term survival in adult patients with primary refractory AML. The proposed risk-scoring system may support clinical decision-making and patient counselling.

4. Different impacts of granulocyte colony-stimulating factor administration on allogeneic hematopoietic cell transplant outcomes for adult acute myeloid leukemia according to graft type.

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We retrospectively evaluated the impacts of using granulocyte colony-stimulating factor (G-CSF) and its timing on posttransplant outcomes for 9766 adults with acute myeloid leukemia (AML) between 2013 and 2022 using a Japanese database. We separately evaluated three distinct cohorts based on graft type: 3248 received bone marrow transplantation (BMT), 3066 received peripheral blood stem cell transplantation (PBSCT), and 3452 received single-unit cord blood transplantation (CBT). Multivariate analysis showed that G-CSF administration significantly accelerated neutrophil recovery after BMT, PBSCT, and CBT. However, it was associated with a higher risk of grades II-IV acute graft-versus-host disease (GVHD) across all graft types. Moreover, an increased incidence of overall chronic GVHD was observed with G-CSF administration in BMT and CBT patients, but not in PBSCT patients. G-CSF administration significantly improved overall survival (OS) and leukemia-free survival (LFS) only following CBT. Regarding the timing of G-CSF, in comparison with late initiation of G-CSF (Days 5-10), early initiation (Days 0-4) did not provide benefits for hematopoietic recovery regardless of graft type. In contrast, late initiation was significantly associated with a lower risk of grades II-IV acute GVHD and better OS and LFS in CBT patients. These data demonstrated that G-CSF administration accelerated neutrophil recovery and increased the risk of grades II-IV acute GVHD across all graft types, but significantly improved survival outcomes but only following CBT. Therefore, routine use of G-CSF should be considered for CBT in adult patients with AML.

5. Toll-Like Receptor Polymorphisms Influence Graft-Versus-Host Disease and Infection Risk After Single-Unit Cord Blood Transplantation for Adults.

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Toll-like receptors (TLRs) play a critical role in innate immunity by recognizing pathogen-associated and damage-associated molecular patterns. Genetic polymorphisms in TLR genes can modulate immune responses and have been implicated in the outcomes of allogeneic hematopoietic cell transplantation (HCT). However, their impact on clinical outcomes after single-unit cord blood transplantation (CBT) remains unclear. We retrospectively analyzed adult patients who underwent single-unit CBT at our institution between January 2005 and March 2023 with available recipient or donor DNA samples. Genotyping of TLR2 (rs3804099), TLR3 (rs3775291), TLR5 (rs5744174), and TLR9 (rs352140) was performed. Associations between recipient and donor TLR polymorphisms and transplantation outcomes-including hematopoietic engraftment, acute and chronic graft-versus-host disease (GVHD), infectious complications, relapse, non-relapse mortality (NRM), and survival-were evaluated using univariate and multivariate analyses. Donor TLR2 rs3804099 and TLR9 rs352140 variants were associated with platelet engraftment rates. Recipient TLR3 rs3775291 TT genotype correlated with increased risk of grades II-IV acute GVHD and invasive fungal infection, while donor TLR5 rs5744174 GG/GA genotypes were linked to higher chronic GVHD incidence. Recipients with TLR9 rs352140 CC genotype exhibited higher bacteri-

al bloodstream infection and NRM rates. No significant associations were found between TLR polymorphisms and overall or disease-free survival. Cytokine analyses revealed distinct profiles according to TLR polymorphisms, including elevated MCP-1 and IL-18 in TLR5 GG/GA donors and lower IL-8 in TLR9 CC recipients, suggesting mechanistic relevance. Our findings demonstrate that recipient and donor polymorphisms in TLR3, TLR5, and TLR9 genes affect GVHD development and infection risk following single-unit CBT in adults. Understanding these genetic influences may guide personalized approaches to improve CBT outcomes.

Publications

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