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 researching the clinical promotion and medical development of hematopoietic stem cell transplantation, with a focus on cord blood transplantation. We are also working on the identification of factors involved in transplant complications using GWAS, with the aim of making transplantation safer. We are also generating pre-clinical study to utilize virus-specific CTL for immune competent patients such as post-transplantation. Our goal is as allogeneic transplantation to be safer therapeutic option and to extend for older patients.

1. Higher Cryopreserved CD34(+) Cell Dose Is Associated with Decreased Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome after Single-Unit Cord Blood Transplantation in Adults Given Prophylactic Ursodeoxycholic Acid and Intravenous Heparin

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Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is one of the most serious complications to occur early after allogeneic hematopoietic cell transplantation (HCT). However, detailed data on VOD/SOS after cord blood transplantation (CBT) are not available. The objective of this retrospective study was to evaluate the incidence, risk factors, and clinical impact of VOD/SOS after single-unit unrelated CBT for adult patients at our institution. We retrospectively evaluated the incidence, risk factors, and outcomes of VOD/SOS after 390 single-unit unrelated CBTs performed in 332 adults under a prophylactic strategy of ursodeoxycholic acid (UDCA) and i.v. heparin at our institution between 1998 and 2021. VOD/SOS was observed in 24 of the 390 CBTs. The cumulative incidence of VOD/SOS was 5.9% at 30 days and 6.2% at 100 days after CBT. Multivariate analysis showed that cryopreserved CD34(+) cell dose >/=1.0 x 10(5)/kg was significantly associated with a decreased risk of VOD/SOS after CBT (hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.12 to 0.91; P = .032). In multivariate analysis, the development of VOD/SOS was significantly associated with higher overall mortality (HR, 6.19; 95% CI, 3.61 to 10.65; P < .001), treatment failure (HR, 4.79; 95% CI, 2.95 to 7.76; P < .001), and nonrelapse mortality (HR, 12.60; 95% CI, 6.90 to 23.00; P < .001). Our study shows that the incidence of hepatic VOD/SOS was relatively low after unrelated single-unit CBT under a prophylactic strategy of UDCA and i.v. heparin. A higher cryopreserved cord blood CD34(+) cell dose was associated with a reduction in VOD/SOS, suggesting that selection of a higher cord blood unit CD34(+) cell dose could be efficient in preventing hepatic VOD/SOS in adults undergoing single-unit CBT.

2. Optimal time and threshold of absolute lymphocyte count recovery as a prognostic factor after single-unit cord blood transplantation in adults.

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We retrospectively evaluated the optimal time and threshold of absolute lymphocyte count (ALC) recovery as a prognostic factor in 174 adult patients who received single-unit cord blood transplantation (CBT) at our institute. We analyzed the impact of ALC >/=300, >/=600, and >/=900/mul by 30 and 60 days on transplant outcomes. Multivariate analysis showed that only ALC >/=300/mul at 60 days was significantly associated with overall mortality (hazard ratio, 0.24; p = 0.001) following CBT. The optimal time point to use ALC recovery as a prognostic tool following CBT could be later than those following adult donor transplantation.

3. Total body irradiation-based versus busulfan-based myeloablative conditioning for single-unit cord blood transplantation in adults.

Konuma, T[1,2]. Ooi, J[2,4]. Monna-Oiwa, M[2]. Isobe, M[2]. Tomonari, A[2,4]. Kato, S[2]. Iseki, T[2,4]. Nannya, Y[1,2,3]. Tojo, A[2,3,4]. Takahashi, S[2,3].
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Comparative studies between total body irradiation (TBI)-based and busulfan-based myeloablative conditioning (MAC) regimens for cord blood transplantation (CBT) have been limited. We retrospectively analyzed the results of single-unit CBT in 333 adult patients who received either TBI-based (n = 258) or busulfan-based (n = 75) MAC regimens at our institute. After adjusting for significant variables in the univariate analysis, there were no significant differences in neutrophil recovery (hazard ratio (HR), 0.88; p = .460), grade III-IV acute graft-versus-host disease (GVHD) (HR: 1.40, p = .410), extensive chronic GVHD (HR: 0.73, p = .380), relapse (HR: 0.61, p = .270), non-relapse mortality (HR: 1.38, p = .420), overall survival (HR: 1.18, p = .637), or event-free survival (HR: 1.08, p = .773), although platelet recovery was lower with marginal significance for the busulfan-based regimen (HR: 0.67, p = .068). In subgroup analysis, TBI-based regimens were superior to busulfan-based regimens in terms of survival for acute lymphoblastic leukemia, but not for myeloid malignancies. Further investigation is warranted even for CBT.

Publications

1. Kato S, Konuma T, Monna-Oiwa M, Isobe M, Takahashi S, Nannya Y. Higher Cryopreserved CD34(+) Cell Dose Is Associated with Decreased Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome after Single-Unit Cord Blood Transplantation in Adults Given Prophylactic Ursodeoxycholic Acid and Intravenous Heparin. *Transplant Cell Ther*. 2022, 28(11),779 e1- e9.
2. Kobayashi S, Kanda Y, Konuma T, Inamoto Y, Matsumoto K, Uchida N, Ikegame K, Miyamoto T, Doki N, Nakamae H, Katayama Y, Takahashi S, Shiratori S, Saito S, Kawakita T, Kanda J, Fukuda T, Atsuta Y, Kimura F. Outcomes of third allogeneic hematopoietic stem cell transplantation in relapsed/refractory acute leukemia after a second transplantation. *Bone Marrow Transplant*. 2022, 57(1),43-50.
3. Konuma T, Harada K, Kondo T, Masuko M, Uchida N, Yano S, Kawakita T, Onizuka M, Ota S, Sakaida E, Miyakoshi S, Ozawa Y, Imamura Y, Kimura T, Kanda Y, Fukuda T, Atsuta Y, Yanada M, Adult Acute Myeloid Leukemia Working Group of the Japanese Society for T, Cellular T. Salvage single-unit unrelated cord blood transplantation for graft failure following initial allogeneic transplantation in adult acute myeloid leukemia: trends in outcomes over the past 20 years. *Bone Marrow Transplant*. 2022, 57(12),1848-50.
4. Konuma T, Kanda J, Uchida N, Nishijima A, Tanaka M, Ozawa Y, Sawa M, Onizuka M, Ota S, Maruyama Y, Kanda Y, Kawakita T, Ara T, Eto T, Nakamae H, Kimura T, Fukuda T, Atsuta Y, Donor/Source Working Group of theJapanese Society for T, Cellular T. Intensified conditioning regimens improved disease-free survival and engraftment after unrelated single-unit cord blood transplantation but not after matched sibling or matched unrelated donor allogeneic hematopoietic cell transplantation. *Hematol Oncol*. 2022,
5. Konuma T, Mizuno S, Harada K, Uchida N, Takahashi S, Eto T, Ota S, Kobayashi H, Katayama Y, Mori Y, Maruyama Y, Onizuka M, Yonezawa A, Kawakita T, Kimura T, Kanda Y, Fukuda T, Atsuta Y, Yanada M, Adult Acute Myeloid Leukemia Working Group of the Japanese Society for T, Cellular T. Reducing Mortality of Single-Unit Unrelated Cord Blood Transplantation for Relapsed Acute Myeloid Leukemia after a Previous Allogeneic Transplantation: A Real-World Retrospective Study Over the Past 19 Years in Japan. *Transplant Cell Ther*.2022, 28(11),777 e1- e11.
6. Konuma T, Monna-Oiwa M, Takano K, Isobe M, Kato S, Takahashi S, Nannya Y. Optimal time and threshold of absolute lymphocyte count recovery

as a prognostic factor after single-unit cord blood transplantation in adults. *EJHaem*. 2022, 3(1),191-8.
7. Konuma T, Ooi J, Monna-Oiwa M, Isobe M, Tomonari A, Kato S, Iseki T, Nannya Y, Tojo A, Takahashi S. Total body irradiation-based versus busulfan-based myeloablative conditioning for single-unit cord blood transplantation in adults. *Leuk Lymphoma*. 2022, 63(5),1191-201.
8. Konuma T, Shimomura Y, Ishiyama K, Ara T, Nakamae H, Hiramoto N, Eto T, Maruyama Y, Nagafuji K, Ishikawa J, Uchida N, Tanaka M, Onizuka M, Ueda Y, Anzai N, Kimura T, Kanda Y, Fukuda T, Atsuta Y. Haploidentical transplantation with post-transplant cyclophosphamide versus single cord blood transplantation for myelodysplastic syndrome: A retrospective study from the Adult Myelodysplastic Syndrome Working Group of the Japanese Society for Transplantation and Cellular Therapy (JSTCT). *Am J Hematol*. 2022, 97(12),E447-E50.
9. Konuma T, Tomonari A, Ooi J, Nagayama H, Kawakita T, Kato S, Isobe M, Monna-Oiwa M, Tojo A, Nannya Y, Takahashi S. Thyrotoxicosis after unrelated cord blood transplantation for adults. *Ann Hematol*. 2022,
10. Matsuda K, Konuma T, Fuse K, Masuko M, Kawamura K, Hirayama M, Uchida N, Ikegame K, Wake A, Eto T, Doki N, Miyakoshi S, Tanaka M, Takahashi S, Onizuka M, Kato K, Kimura T, Ichinohe T, Takayama N, Kobayashi H, Nakamae H, Atsuta Y, Kanda J, Yanada M. Comparison of transplant outcomes between haploidentical transplantation and single cord blood transplantation in non-remission acute myeloid leukaemia: A nationwide retrospective study. *Br J Haematol*. 2022,
11. Mizuno S, Takami A, Kawamura K, Shimomura Y, Arai Y, Konuma T, Ozawa Y, Sawa M, Ota S, Takahashi S, Anzai N, Hiramoto N, Onizuka M, Nakamae H, Tanaka M, Murata M, Kimura T, Kanda J, Fukuda T, Atsuta Y, Yanada M. Favorable Outcome with Conditioning Regimen of Flu/Bu4/Mel in Acute Myeloid Leukemia Patients in Remission Undergoing Cord Blood Transplantation. *Transplant Cell Ther*. 2022, 28(11),775 e1- e9.
12. Okada Y, Nakasone H, Konuma T, Uchida N, Tanaka M, Sugio Y, Aotsuka N, Nishijima A, Katsuoka Y, Ara T, Ota S, Onizuka M, Sawa M, Kimura T, Fukuda T, Atsuta Y, Kanda J, Kimura F. Ideal Body Weight Is Useful For Predicting Neutrophil Engraftment and Platelet Recovery for Overweight and Obese Recipients in Single-Unit Cord Blood Transplantation. *Transplant Cell Ther*. 2022, 28(8),504 e1- e7.
13. Saito K, Sato T, Notohara K, Nannya Y, Ogawa S, Ueda Y. Complete Bone Marrow Necrosis with Charcot-Leyden Crystals Caused by Myeloid Neoplasm with Mutated NPM1 and TET2. *Intern Med*. 2022, 61(21),3265-9.
14. Takano K, Konuma T, Monna-Oiwa M, Isobe M, Kato S, Takahashi S, Nannya Y. Prognostic impact of switching from cyclosporine to corticosteroids early after single cord blood transplantation. *Ann Hematol*. 2022, 101(10),2377-8.
15. Yanada M, Harada K, Shimomura Y, Arai Y, Konuma T. Conditioning regimens for allogeneic hematopoietic cell transplantation in acute myeloid leukemia: Real-world data from the Japanese registry studies. *Front Oncol*. 2022, 121050633.
16. Yanada M, Yamasaki S, Konuma T, Mizuno S, Uchida N, Onai D, Fukuda T, Tanaka M, Ozawa Y, Eto T, Ikegame K, Sawa M, Katayama Y, Kawakita T, Onizuka M, Kanda Y, Ichinohe T, Atsuta Y, Yano S. Age and allogeneic hematopoietic cell transplantation outcomes in acute myeloid leukemia. *Int J Hematol*.2022,