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 performed at the Department of Hematology/Oncology, 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. Should a matched sibling donor still be considered the primary option for allogeneic hematopoietic cell transplantation in patients over 50 years of age with myelodysplastic syndrome?

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Human leukocyte antigen (HLA)-matched sibling donors (MSDs) are the preferred choice for allogeneic hematopoietic cell transplantation (HCT). However, as myelodysplastic syndrome (MDS) is most frequently diagnosed in the elderly, MSDs are also likely to be of advanced age. It is unclear whether an MSD should be considered the primary choice for allogeneic HCT in elderly patients with MDS. We retrospectively compared survival and other outcomes in 1787 patients with MDS over 50 years of age and receiving allogeneic HCT between 2014 and 2020, using either MSD (n=214), 8/8 allele-matched unrelated donor (MUD) (n=562), 7/8 allele-MUD (n=334), or unrelated cord blood (UCB) (n=677) in Japan. In multivariate analysis, compared to MSD transplants, the risk of relapse was significantly lower following 8/8MUD transplants (hazard ratio [HR], 0.74; P=0.047), whereas non-relapse mortality was significantly higher following UCB transplants (HR, 1.43; P=0.041). However, donor type did not determine overall survival, disease-free survival, or graft-versus-host disease (GVHD)-free, relapse-free survival, but chronic GVHD-free, relapse-free survival was better after UCB (HR, 0.80; P=0.025) and 8/8MUD (HR, 0.81; P=0.032) compared to MSD transplants. Our study demonstrated that MSDs are not superior to alternative HCT methods, such as 8/8MUD, 7/8MUD, or UCB, in this population.

2. Comparison of allogeneic transplant outcomes between matched sibling donors and alternative donors in patients over 50 years of age with acute myeloid leukemia: 8/8 allele-matched unrelated donors and unrelated cord blood provide better leukemia-free survival compared with matched sibling donors during non-remission status

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resenting for: the Adult Acute Myeloid Leukemia and Donor/source Working Groups of the Japanese Society for Transplantation and Cellular Therapy
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Acute myeloid leukemia (AML) is the most common indication for allogeneic hematopoietic cell transplantation (HCT). The increased availability of alternative donor sources has broadened donor types for older patients without HLA-matched sibling donors (MSD). It is uncertain if an MSD should be the first option for allogeneic HCT in patients with AML over 50 years of age. The objective of this study was to compare survival and other posttransplant outcomes between MSDs, 8/8 allele-matched unrelated donors (MUDs), 7/8 allele-MUDs, unrelated cord blood (UCB), and haploidentical donors for patients with AML over 50 years of age. We conducted a retrospective study to compare outcomes in 5,704 patients with AML over 50 years of age and receiving allogeneic HCT between 2013 and 2021, using either MSD, 8/8 allele-MUD, 7/8 allele-MUD, UCB, or haploidentical donors in Japan. Complete remission (CR) and non-remission at HCT were analyzed separately for all analyses. In total, 3041 patients were CR, and 2663 patients were non-remission at the time of HCT. In multivariate analysis, donor type did not determine overall survival, irrespective of disease status at HCT. Leukemia-free survival (LFS) was significantly better for 8/8 allele-MUD (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.64 to 0.93; P = 0.005) and UCB (HR, 0.76; 95% CI, 0.65 to 0.88; P = 0.001), but not for 7/8 allele-MUD (HR, 0.97; 95% CI, 0.79 to 1.19; P=0.794), and haploidentical donor (HR, 0.86; 95% CI, 0.70 to 1.05; P=0.146) compared to the MSD group in non-remission status. However, donor type did not determine LFS among CR status. Relapse rates were significantly lower for 8/8 allele-MUD and UCB, whereas non-relapse mortality was higher for UCB compared to the MSD group among both CR and non-remission status. Our registry-based study demonstrated that MSDs do not lead to superior survival compared to alternative donors for patients with AML over 50 years of age. Furthermore, 8/8 allele-MUDs and UCB provide better LFS compared with MSDs during non-remission status. Therefore, MSD is not necessarily the best donor option for allogeneic HCT in this population.

3. Development of ex vivo culture methods for primary tumor specimens derived from patients of myeloid malignancies.

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High throughput drug sensitivity screening (DSS) using patient-derived primary tumor specimens (PTS) are one of the most updated methods in current precision medicine. Recently, we have developed an experimental platform in which completely robotized handling of PTS is installed. They provide us with capability of conducting high throughput drug screening equipped with multicolor flow cytometry analyses upon ex vivo cultured PTS prepared on miniaturized 384-well-plate system. Even with those extremely modernized system, paucity of available primary cells is a yet-to-be-solved issue, considering numbers of candidate drugs, and types of clinical questions. The issue is more valid for PTS of myelodysplastic syndrome (MDS) , since the disease is characterized by its lower ratios of blast cells, and relatively lower cell numbers than highly proliferative acute myeloid leukemia (AML) cells. In order to expand possibility of those AML/ MDS PTS for more advanced applications, we have performed experiments to side-by-side compare different ex vivo culture methods. At Clinical Precision Research Platform, we have already collected 159 different PTS aliquoted into 1495 cryovials. They are ongoingly used either in the automated DSS experiments, OMICS-analyses, or in this ex vivo culture assays. We have discovered that 1. Short-term culture protocols (up to 7 days) optimized for the current DSS assays make a few differences regardless of changed concentrations of serum or other supplements for culture media. 2. Use of stromal feeder cells prevails other conventional stroma-free culture methods that are currently utilized for normal hematopoietic stem cells. Moreover, 3. Recently, we installed the most updated culture methods to challenge for stroma-free, serum-free ex vivo culture system optimized for PTS. The idea for the updated culture media is derived from ongoing research projects by collaborators regarding normal hematopoietic stem cell culture. Initial data on this topic is continuously fueling our research motivations, day by day. Details of those findings will be followingly updated.

Publications

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