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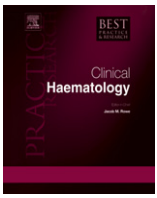

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Can double-cord transplants provide a more potent graft-vs-leukemia effect?

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When an HLA-identical sibling is unavailable in a patient who needs allogeneic transplant, physicians are faced with the choice of several alternative donor types: matched unrelated donors, mismatched unrelated donors, and single- or double-unit umbilical cord (UCB) blood grafts. UCB transplant is a viable alternative for many patients, though adolescents and adults are limited to double-unit grafts due to dose limitations. Double-unit UCB transplants after myeloablative conditioning regimens have been linked with lower relapse rates than other donor types, though they are also associated with longer time to hematopoietic engraftment and subsequent higher rates of non-relapse mortality. The role of double-unit UCB transplants in reducing relapse incidence is less clear with reduced-intensity conditioning regimens.

Introduction

Allogeneic hematopoietic stem cell transplant (allo-HCT) is the only potential curative treatment for acute myeloid leukemia (AML). However, only 30% of patients will have a human leukocyte antigen (HLA)-matched sibling donor (MSD) and are able to proceed with allo-HCT. Matched unrelated donors (MUD) through registries are a great source for patients without HLA-identical siblings; however, patients from diverse ethnic backgrounds may not be able to rapidly identify a suitably MUD. This results in an estimated 5000 patients with AML each year who are candidates for alternative donor transplant, which includes mismatched unrelated donors (MMUD), umbilical cord blood transplant (UCBT), or haplo-identical stem cell transplant.

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An analysis completed by the Center for International Blood and Marrow Transplant Research (CIBMTR) in collaboration with Eurocord compared patients with unrelated bone marrow (BM, $n = 472$) or peripheral blood stem cells (PBSC, $n = 888$) to UCB ($n = 165$) HCT adults with acute leukemia [1]. In this study, allele-level HLA typing was performed for the adult donors at A, B, C, and DRB1 loci and either 8/8 and 7/8 matched donors were included. All UCB units were HLA-typed at the antigen level for the A and B loci, with allele-level typing for DRB1. UCB units matched at 4–6/6 loci were included. For patients with active disease at allo-HCT, matched related transplant produced the best leukemia-free survival (LFS) rates. However, mismatched unrelated peripheral or bone marrow and UCB transplant LFS rates were similar (~34%). This study shows that for patients who do not have an MSD available, UCB should be considered as an alternative donor source.

A study by Cohen et al. [2] used data from 3 main cord blood registries: CIBMTR, Eurocord-Netcord, and the New York Blood Center National Cord Blood Program. Among 514 leukemia patients who received myeloablative conditioning (MAC) and single-unit UCBT, the 1-year survival rate was 37%, which is comparable to rates observed with other donor sources [2]. Overall survival (OS) was lower with older age of the patient, advanced disease at the time of transplant, and having a transplant at a center with limited experience.

While those studies confirm that UCBT should be considered in patients when there is no MSD available as an alternative source, cell dose in single-unit UCBT remains the main limitation to offering UCBT in many larger adolescents or adult patients. Double-unit UCBT (dUCBT) has been adopted by many transplant centers as a strategy to overcome this limitation.

University of Minnesota experience

The University of Minnesota has been a pioneer in the dUCBT transplant field. An analysis done in collaboration with the Fred Hutchinson Cancer Research Center used data from 536 patients with hematologic malignancy who underwent transplant from different donor sources including either MSD, MUD, MMUD, and dUCB [3]. The median age of the dUCB recipients was younger (25 years) when compared to MSD (40 years), MUD (31 years), and MMUD (31 years) recipients. However, the maximum age for recipients of a MAC regimen and dUCBT was 45 years. The study included patients with acute lymphoblastic leukemia (ALL), AML, chronic myeloid leukemia (CML), and myelodysplastic syndrome (MDS) [3]. The diseases were similarly distributed across donor types, except that more CML patients received MMUD and MUD transplants. Those with high-risk disease were similarly distributed among the four donor sources. Median number of years of survival was shorter for dUCBT, but this may be due to much shorter follow-up time. Time to cell engraftment among different donor types was analyzed [3]. Time to neutrophil engraftment $\geq$500 cells/μL was longer in dUCB recipients than for those who had other donor sources (median of 26 days vs 16 days for MSD recipients and 19 days for MUD and MMUD recipients). Platelet engraftment was also much slower for the dUCB recipients, but was similar for other donor types. Patients who received dUCBT also had higher transplant-related mortality (TRM) rates than those who received transplants from other donor types, but these patients also enjoyed much lower relapse incidence (13% vs ~35%) [3]. As most transplant-related deaths occurred within the first 100 days after transplant for dUCBT recipients, relapse incidence was recalculated after day 100. Double UCBT recipients still showed lower relapse rates compared to other donor type recipients. Furthermore, LFS was similar (~43%) among different donor sources at 3 years post-transplant.

These data clearly suggest that using dCBT induces similar LFS in comparison to MSD and MUD transplants in adults after myeloablation with cyclophosphamide and total body irradiation-based conditioning regimens. However, more studies are needed to understand the biology behind the lower relapse incidence for dUCBT patients.

A study by Verneris et al. [4] compared relapse risk after single UCBT (sUCBT) or dUCBT in acute leukemia patients to address whether the low relapse rates are attributable to UCB in general or double-unit transplants. The decision to use dUCBT was purely based on dose availability. Before 2002, the dose requirement was 1.5×10^7/kg total nucleated cell dose. After 2002, this requirement was increased to 2.5×10^7/kg total nucleated cell dose. After 2004, if the patients had a 6 out of 6 match for the cord blood, the dose requirement was 3.4×10^7/kg, and if they had one mismatch, the dose