

Reduced-Intensity Preparative Regimen for Cord Blood Transplantation

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Hematopoietic stem cell transplantation is used to treat patients with hematologic malignancies. Blood stem cells for transplantation are obtained from donor bone marrow, peripheral blood, or umbilical cord blood (CB). Before receiving a transplant, patients first must undergo myeloablative conditioning regimens to remove diseased bone marrow and to create an immunosuppressive environment that allows engraftment of donor stem cells and reconstitution of a normal blood system. Donors and recipients are matched for human leukocyte antigen (HLA) alleles to reduce graft-versus-host disease (GVHD), which occurs when donor cells mount an immune response against recipient cells. HLA mismatches are better tolerated using CB transplant (CBT) compared to other sources of stem cells. For patients who lack a donor HLA match or who cannot tolerate traditional transplant regimens, CBT offers an effective therapy for advanced or high-risk hematologic malignancies.

To obtain enough stem cells for engraftment, patients receive CB from two donors sequentially. Previous studies by Dr. Colleen Delaney and colleagues from the Clinical Research Division determined that double-unit CBT had a similar leukemia-free survival (53%, 95% confidence interval 41-59%) to other sources of adult stem cells, including HLA-matched donors (related or unrelated), or HLA-mismatched unrelated donors (Brunstein *et al.*, 2010). However, there is a delay in hematopoietic recovery and a higher risk of non-relapse mortality for double-unit CBT compared to other sources of blood stem cells.

For older patients and those with comorbidities, reduced-intensity conditioning (RIC) regimens promote engraftment through immunosuppression, but result in less tissue damage, inflammation, and lower rates of GVHD than traditional myeloablative regimens. Optimal conditions for RIC in CBT have not been established. Antithymocyte globulin (ATG), an infusion of rabbit antibodies against T-cells, has been used in some RIC CBT regimens to reduce acute GVHD. However, ATG can result in delayed reconstitution of T-cells, an increased risk of post-transplant EBV-driven lymphoproliferative disorder, an increased risk of viral infections, and decreased graft-versus-tumor effect. Drs. Fabiana Ostronoff, Filippo Milano, Colleen Delaney and colleagues in the Clinical Research Division evaluated a RIC regimen without ATG for CBT in advanced and high-risk hematologic malignancies where no donor match was available. The primary goal of their study was

to estimate the probability of overall survival at one year for a RIC without ATG, to establish a benchmark to compare as an estimate for future trials.

Between February 2006 and January 2011, 30 patients with various high-risk advanced hematologic malignancies underwent double-unit CBT with a RIC regimen without ATG. Prior to CBT, patients were treated for four days with fludarabine, a purine analog chemotherapeutic agent; a single dose of cyclophosphamide, an alkylating agent; and total body irradiation at doses of 200-450 cGy, depending on risk of graft failure and previous treatments. Twenty-seven of 30 patients recovered their neutrophil count after transplant between six to 40 days, median 17 days. Of the three patients who did not reach engraftment, two died from multi-organ failure and one died of hemorrhagic meningitis. Of note, two of these patients were considered a high-risk of graft failure.

Compared to other RIC CBT regimens that include ATG, the incidence of acute GVHD was similar in this RIC CBT regimen without ATG; 13 of 28 patients had a grade II GVHD. Probability of chronic GVHD was estimated at 2 years at 18%, although follow up was limited in some patients and they are still at risk of developing chronic GVHD. Even though one or two HLA alleles were mismatched for the two CB units, GVHD incidence was similar to that seen with HLA-matched bone marrow or peripheral blood transplants. There were 11 cases of non-relapse mortality, with estimated probability of 29% at one year, which is similar to non-relapse mortality in RIC CBT performed with ATG included in the treatment regimen. Eight patients relapsed after transplant. Of those who relapsed, only two survived at the last follow-up. 13 patients had survived the RIC CBT at the last study follow-up (range of 114-1303 days post transplant). From this data, the estimated overall survival was 53% at 1 year, which matched previous studies examining double-unit CBT (Brunstein *et al.*, 2010).

The results of this small study suggest that removing ATG from a RIC regimen does not affect graft failure or GVHD incidence for double-unit CBT. Larger studies with longer follow-up are needed to confirm these findings. Importantly, the RIC regimen also needs to be optimized to minimize graft failure, improve hematopoietic recovery and reduce non-relapse mortality to improve the efficacy of CBT.

[Ostronoff F., Milano F., Gooley T., Gutman J.A., McSweeney P., Petersen F.B., Sandmaier B.M., Storb R., and Delaney C.](#) 2012. Double umbilical cord blood transplantation in patients with hematologic malignancies using a reduced-intensity preparative regimen without antithymocyte globulin. *Bone Marrow Transplantation*. Epub ahead of print, doi: 10.1038/bmt.2012.243

Also see: [Brunstein C.G., Gutman J.A., Weisdorf D.J., Woolfrey A.E., Defor T.E., Gooley T.A., Verneris M.R., Appelbaum F.R., Wagner J.E., and Delaney C.](#) 2010. Allogeneic hematopoietic cell transplantation for hematologic malignancy: relative risks and benefits of double umbilical cord blood. *Blood*. 116:4693-9.



Dr. Colleen Delaney
