CIBMTR Best Abstract Awards for Clinical Research

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PHASE II TRIAL OF NON-MYELOABLATIVE CONDITIONING (NST) DOUBLE UMBILICAL CORD BLOOD TRANSPLANTATION (DUCBT) FROM UNRELATED DONORS IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES: RESULTS OF BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK (BMT CTN) PROTOCOL 0604

Brunstein, C.G.[1], Carter, S.[2], Fuchs, E.J.[3], Karanes, C.[4], Devine, S.[5], Aljitawi, O.[6], Cutler, C.[7], Ballen, K.K.[8], Thompson, J.[2], O'Donnell, P.V.[9], Eapen, M.[10] [1] University of Minnesota, Minneapolis, MN; [2] Emmes Corporation, Rockville, MD; [3] The Johns Hopkins University, Baltimore, MD; [4] City of Hope National Medical Center, Duarte, CA; [5] Ohio State University, Columbus, OH; [6] University of Kansas, Kansas City, KS; [7] Dana Farber Cancer Institute, Boston, MA; [8] Massachusetts General Hospital, Boston, MA; [9] Fred Hutchinson Cancer Research Center, Seattle, WA; [10] Medical College of Wisconsin, Milwaukee, WI

We prospectively evaluated survival after NST dUCBT for poor risk acute leukemia or lymphoma (excluding mantle cell) in patients without a suitably matched related donor. Eligible were patients aged ≤ 70 years with adequate organ function (ejection fraction > 35%; lung function > 50% predicted; total bilirubin ≤ 2.5 mg/dl, liver enzymes < 5 × upper limit of normal; CrCl > 40 mL/min/1.73m^2), performance score (PS) ≥ 60, and > 3 months after prior autologous transplant. The preparative regimen consisted of fludarabine 40 mg/m^2 IV days –6 to -2, cyclophosphamide 50 mg/kg IV day -6, total body irradiation 200 cGy day –1 and immunosuppression with a calcineurin inhibitor and mycophenolate mofetil. G-CSF started at day +1. All patients received dUCB grafts HLA-matched 4-6/6 (A and B at antigen level, DRB1 allele level) to the patient and to each other. Fifty-four patients were enrolled from 16 centers; 4 of 54 patients were excluded due to progressive disease prior to dUCBT (n = 3) and 1 withdrew consent. The median age was 58 yrs (range, 16-69) and weight, 79kg (range, 46-119). Thirty-six patients had acute leukemia (64% were in CR1) and 14 patients had lymphoma. Six patients (12%) had a prior autologous transplant. The median infused combined nucleated cell dose was 4.2 × 10^7/kg (2.3-13.6). Fifty-three percent of the units were 4/6 and 39% were 5/6 HLA-matched to the recipient; 66% of patients received at least one 4/6 HLA-matched unit. Most patients (80%) had PS 90-100. The median follow-up of survivors was 364 days (range, 154-381). The 6-month probability of overall survival was 72% (95%CI, 56-83%) and progression-free survival 63% (95% CI, 48-76%). The cumulative incidence of treatment-related mortality at day-180 was 20% (95%CI, 8-31%) and relapse/progression, 14% (95%CI, 4-24%). Eighteen patients died and relapse/progression was the most common cause (N = 9). The cumulative incidence of grade II-IV acute GVHD at day 56 is 36% (95%CI, 22-50%) and grade III-IV 10% (95%CI, 2-19%) and chronic GVHD at 180 days was 13% (5%CI, 3-24%). The cumulative incidence of neutrophil recovery at day 56 was 94.0% (95%CI, 87-100.0%) at a median time of 17 days (range, 6-45). Three patients had primary and 1 secondary graft failure. These data demonstrate that NST dUCBT is safe, reproduced results from single centers in the multicenter setting, and establishes the framework for randomized trials to study alternative donor NST transplantation for hematologic malignancies.

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PHASE II TRIAL OF NON-MYELOABLATIVE CONDITIONING AND PARTIALLY HLA-MISMATCHED (HLA-HAPLOIDENTICAL) BONE MARROW TRANSPLANTATION (BMT) FOR PATIENTS WITH HEMATOLOGIC MALIGNANCIES: RESULTS OF BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK (BMT CTN) PROTOCOL 0603

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We evaluated survival after nonmyeloablative, HLA-haploidentical BMT and GVHD prophylaxis incorporating high dose, post-transplantation cyclophosphamide (Cy) for patients with poor risk leukemia or lymphoma who lacked a HLA-matched related donor. The trial enrolled 55 patients from 17 centers and 52 proceeded to transplantation. Their median age was 51 years (range, 7-70); 32 were male, and 42, Caucasian. Diagnoses included acute myeloid (10 in CR1, 13 in CR ≥ 2), acute lymphocytic (3 in CR1, 3 in CR ≥ 2) biphenotypic/undifferentiated leukemia in CR (n = 3) and, relapsed/chemosensitive Hodgkin (n = 8), mantle cell (n = 3), large cell (n = 8), and marginal zone B cell lymphoma (n = 1). Thirty-nine patients had performance status ≥ 90%, and 12 patients had failed prior autologous SCT. Median donor age was 43 years and the median mismatch, 5/10 HLA alleles in the graft-versus-host direction and 4/10 alleles in the host-versus-graft direction. Patients were conditioned with Cy (14.5 mg/kg IV, day -6, -5), fludarabine (30 mg/m^2 IV, day -6 to -2), total body irradiation (200 cGy, day -1) followed by infusion of T-cell replete bone marrow. GVHD prophylaxis consisted of Cy 50 mg/kg IV on day +3 and +4, mycophenolate mofetil, day +5 to +35, and tacrolimus, day +5 to +180. Filgrastim was given from day +5 until neutrophil recovery. The median times to > 0.5 × 10^9/L neutrophils and platelets ≥ 20 × 10^9/L, were 16 and 21 days, respectively. The median donor chimerism in marrow/blood at day +28 was 100% (range, 70-100%), and T cell chimerism, 100%. One patient experienced primary graft failure and none, secondary graft failure. The day +56 incidence of acute grade II GVHD was 31% (95% CI, 18-44%) and day +180 chronic GVHD, 11% (95% CI, 1-22%). No patient experienced grade III-IV acute GVHD. The day +180 incidences of relapse/progression and non-relapse mortality were 19% (95% CI, 7-32%) and 5% (95% CI, 0-13%), respectively. Ten patients experienced relapse/progression and there were 13 deaths: relapse/progression (n = 8); infection (n = 2); graft failure (n = 1); unknown (n = 2). With a median follow-up of surviving patients of 294 days (range 76-650), the 6-month probabilities of overall and event-free survival are 82% (95% CI, 65-91%) and 75% (95% CI, 59-86%), respectively. These results confirm nonmyeloablative, HLA-haploidentical BMT is feasible, associated with low toxicity and these data may be used to plan multi-center trials to identify the optimal alternative donor.

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MOST CLOSELY HLA-MATCHED ALLOGENEIC VIRUS SPECIFIC CYTOTOXIC T-LYMPHOCYTES (CTL) TO TREAT PERSISTENT REACTIVATION OR INFECTION WITH ADENOVIRUS, CMV AND EBV AFTER HEMOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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Adoptive transfer of CTLs can reconstitute antiviral immunity to EBV, CMV and Adv in allogeneic hemopoietic stem cell transplant (HSCT) recipients. However, the time taken to prepare patient-specific products and the lack of virus-specific T-cells in cord blood and seronegative donors restricts application. As part of the NHLBI Specialized Centers for Cell-Based Therapy, we are evaluating in a multicenter setting whether infusion of "off the shelf" closely HLA-matched allogeneic CTLs (CHM-CTLs) will overcome this limitation and prove feasible, safe and effective in HSCT recipients with infection refractory to standard therapy. Using the NHLBI Production Assistance for Cellular Therapies program, we manufactured and tested > 30 multivirus lines, which were polyclonal, comprising CD4+ (median 10%) and CD8+ (median 83%) T-cells with