School of Medicine, Indianapolis, IN; 2Department of Medicine, Division of MRD or unrelated (MUD) donor following cyclophosphamide, (median age, 55 years) received PBMCs from a matched related myeloablative conditioning, monocytes are the initial donor cells analyze in the early (first 2 weeks) post-transplant period. After allogeneic cells in humans, partially because there are few cells to analyze in the early (first 2 weeks) post-transplant period. After myeloablative conditioning, monocytes are the initial donor cells identified in recipients’ blood, followed by polymorphonuclear leukocytes and then lymphocytes. Forty-nine consecutive patients with hematological malignancies (median age, 55 years) received PBMCs from a matched related (MRD) or unrelated (MUD) donor following cyclophosphamide, 60 mg/kg on days –6 and –7 (total dose 120 mg/kg) and fludarabine, 25 mg/m² for 5 consecutive days (day –5 through day –1; total dose, 125 mg/m²). GVHD prophylaxis consisted of cyclosporine (n=33) or cyclosporine + mycophenolate mofetil (n=16). Acyclovir, fluconazole and quinolone prophylaxis were provided and freshly harvested, non-manipulated PBMCs were infused within 24 hours of collection. One patient with chronic lymphocytic leukemia (CLL) and a pre-transplant lymphocyte count of >150,000/μm³ (considered an outlier) was removed from the analysis. 5 databases (Excel®, MS, Redwood, CA) was utilized to record white blood counts (WBC) obtained from the computerized medical record; each patient’s total WBC, neutrophil, lymphocyte, and monocyte percentages were recorded from day –7 to day +30. Cumulative data were plotted using S-Plus® software (Insightful, Seattle, WA) and median times to peak percentages were determined. Patients who received conventional conditioning and similar grafts prior to transplantation for hematologic malignancies (AML or MDS) over a similar time period (n=46) were studied and engraftment patterns compared. The following phenomena were observed after nonmyeloablative transplantation: (1) no ‘bump’, (increase in the peripheral WBC) the day following cell infusion; (2) resolution of neutropenia at a median of 12 days after MUD transplants and 15 days after MRD transplants (p=0.778); (3) median peak lymphocyte, monocyte and polymorphonuclear percentages occurred 9, 12 and 23 days post-infusion, respectively. Early disappearance of infused cells from the circulation and relative expansion of lymphocytes preceding the emergence of monocytes and polymorphonuclear cells suggests that relatively quiescent state of the infused donor cells by reprogramming is followed by an immunologically active process after truly non-myeloablative cyclophosphamide/fludarabine conditioning.

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EARLY EXPANSION OF LYMPHOCYTE CELLS PRECEDES MYELOID ENGRAFTMENT FOLLOWING HEMATOPOIETIC CELL TRANSPLANTATION USING TRULY NONMYELOABLATIVE CYCLOPHOSPHAMIDE/FLUDARA-BINE CONDITIONING

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Little is known regarding the mechanism of engraftment of autologous tissue in humans, particularly because there are few cells to analyze in the early (first 2 weeks) post-transplant period. After myeloablative conditioning, monocytes are the initial donor cells identified in recipients’ blood, followed by polymorphonuclear leukocytes and then lymphocytes.

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NON-MYELOABLATIVE CONDITIONING THERAPY WITH FLUDARABINE, CYCLOPHOSPHAMIDE AND ATG ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM HLA-IDENTICAL SIBLING DONOR IN PATIENTS WITH SEVERE APLASIA ANEMIA (SAA)

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Allogeneic bone marrow transplantation (BMT) from an HLA-identical sibling is a curative form of therapy for patients with acquired severe aplastic anemia. Survival has significantly improved over the past 3 decades. The actuarial risk of rejection has been reduced to about 7%. Improved results with survival in excess of 90% have been reported. Current preparative therapies are associated with early and late sequelae such as acute and chronic graft-versus-host disease (aGVHD or cGVHD, respectively) and secondary tumors. In two patients (6 years and 11 years old) with SAA, who had an HLA-identical sibling donor, but could not proceed with myeloablative therapy at the time of transplant for various reasons (delay in results of chromosomal stability and fragility in one patient and abnormal pulmonary function in the second), had a non-myeloablative preparative regimen with Fludarabine (30 mg/m²×4 doses) Cyclophosphamide (5 mg/kg×4 doses) and rabbit ATG (1.5 mg/kg×4 doses) followed by an unmanipulated allogeneic BMT. Graft versus host disease prophylaxis consisted of Cyclosporine from day –1 and Methotrexate 15 mg/m² on day +1 and 10 mg/m² on days +3, +6, +11 after transplant. Myeloid engraftment occurred on day +15 and day +28. The time to a platelet count >20,000 unsupported was +11 days and +29 days. No transplant-related toxicities, including mucositis or alopecia, were recorded. There were no signs for aGVHD or cGVHD. The patients continue with full donor chimerism 31 months and 6 months post transplant, respectively. This data suggests that a non-myeloablative, immunosuppressive regimen is sufficient to provide a stable engraftment in patients with SAA. This approach may be associated with decreased transplant-related short- and long-term toxicities. A larger study is needed to fully evaluate the outcome and toxicities profile associated with this conditioning.

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INFLUENCE OF INTERLEUKIN-6 (IL-6) GENE POLYMORPHISM ON THE OUTCOME OF patients UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION

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BACKGROUND: IL-6 is an important mediator of inflammation and its production depends on the functional IL-6 gene polymorphism (IL-6-174 G/C). Allele G expression is associated with higher IL-6 production. The polymorphism of recipient and/or donor might influence immunological reactions after allogeneic stem cell transplantation (SCT), particularly graft vs. host disease (GvHD) and graft vs. tumor (GvT) one.

AIM OF STUDY: To assess the influence of recipient/donor functional IL-6 gene polymorphism on the development of acute/chronic GvHD, tumor relapse and mortality.

PATIENTS AND METHODS: 56 patients were allografted from HLA-identical related donor. 54 recipients (96%) underwent the procedure because of incurable hematological malignancy and 31 ones (59%) after reduced intensity conditioning (RIC). IL-6-174 G/C genotyping of recipients/donors was provided by the use of polymerase chain reaction with sequential specific primers (PCR-SSP). The influence of GvHD development, tumor relapse and mortality on the IL-6-174 G/C allele manifestation in recipients/donors was assessed by the methods of univariate as well as multivariate statistical analysis (t-test, chi-square, log-rank).

RESULTS: Statistical analysis did not confirm the significant influence of functional IL-6 gene polymorphism of recipients/
267 REDUCED RISK OF RELAPSE IN PEDIATRIC PATIENTS AFTER DOUBLE UNIT CORD BLOOD TRANSPLANTATION! A SINGLE INSTITUTION EXPERIENCE

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Unrelated umbilical cord blood transplantation (UCBT) has become a standard therapeutic option for pediatric patients who may benefit from hematopoietic stem cell transplantation but lack an adequate HLA-identical related donor. UCBT has the advantages of rapid availability and presumably lower risk of severe, acute GVHD despite donor-recipient HLA disparity. Double-unit UCBT (DUCBT) extends access to transplantation for patients who were previously disqualified on the basis of low cell dose in a single unit. Recent studies report high engraftment rate, acceptable rates of severe acute GVHD and acceptable rates of transplantation-related mortality with DUCBT. (Barker Blood. 2005;105:1343-1347). It is unknown, however, whether patients with advanced hematological malignancies and patients with severe co-morbidities would benefit from DUCBT. DUCBT was given to 7 patients with advanced hematological malignancies (AML, n=3, refractory n=1, 2CR n=1, 3CR n=1, ALL, n=4; 1CR Ph+ n=1, 2CR Ph+ n=1, both MRD+, 2CR n=2). The males/female ratio was 5/2. Ages were 5.2-15 yrs (median 14 yr). Five of seven were non-Caucasian (71%). Co-morbidities included invasive fungal infection (n=3), acute pancreatitis (n=1), and bulbar paralysis (n=1). Conditioning regimes were FBBI and melphalan (n=3) and fludarabine with melphalan (n=4). Myeloid engraftment occurred in all patients. The median time to an absolute neutrophil count >500 was 34 days (range 26-74 days). Three patients remained platelet transfusion dependent after day 100. In the remaining 4 patients the median time to a platelet count >20,000 unsupported was 51 days (range 44-69 days). All patients (100%) experienced Grades II-III acute GVHD. There were no patients with Grade IV GVHD and no deaths from acute GVHD. Four patients developed extensive chronic GVHD of the skin only. The 100 day transplant related mortality was 0%. One patient died on day +200 from respiratory failure secondary to multiple recurrent viral infections (CMV, Parainfluenza type 3, and herpes simplex virus). None of the patient suffered relapse. The disease-free survival is 80% with a median day +405 post transplant (range 137-1126). The observation that DUCBT may be associated with a reduced risk of relapse in patients with high-risk leukemia deserves further evaluation. Larger studies will be needed to confirm the clinical observation and investigate what are the potential mechanisms by which DUCBT could mediate an anti-leukemic effect.

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