OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA IN THIRD COMPLETE REMISSION (CR3): A VITAL ROLE FOR GRAFT-VERSUS-HOST-DISEASE/ GRAFT-VERSUS-LEUKEMIA EFFECT IN SURVIVAL

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Children with acute lymphoblastic leukemia (ALL) who suffer 2 relapses could be salvaged by hematopoietic stem cell transplantation (HSCT) provided they respond to the pre HSCT chemotherapy and enter remission. However, these patients are at very high risk for post HSCT relapse and also at a higher risk for transplant related mortality (TRM). Our objective, herein, was to review the outcome of children (0-18years) with ALL who received allogeneic HSCT in third complete remission (CR3) at our institute. From January 1994 – August 2005, twenty-two consecutive children in CR3 received HSCT in our institution. Conditioning regimens included single dose VP16 (60mg/kg IV over 4 hours) and fractionated total body irradiation (TBI; 1200cGy) in six fractions over 3 days (VP16/TBI) in 10 patients and cyclophosphamide 50mg/kg IV over 1 hour daily for 4 days followed by the same dose of TBI (CY/TBI) in 12 patients. Almost all children received cyclosporine A and a short course of methotrexate for graft-versus-host disease (GVHD) prophylaxis, and all patients were in complete morphological remission prior to HSCT. Median age was 8.4 years (range 3.1-15.4). Donor sources were as follows: matched sibling donor (MSD), 8; matched unrelated donor (MUD) 6; one antigen mismatch related donor (MMRD) 4; one antigen mismatch unrelated donor (MMUD) 3 and one patient received 1 antigen mismatched cord progenitor stem cells. White cell engraftment was successful at a median of 18 days (range 9-29). Ten patients died of TRM, seven relapsed, one died from other causes and four patients are long term survivors at a median follow up of 3.7 years (range 1-10.2). All patients who did not develop clinical acute or chronic GVHD relapsed and died. Event free survival was (EFS 19% ± 4%). Three out of the 4 survivors received MMUD and all 4 survivors had moderate to severe acute GVHD and three had chronic GVHD, limited in two and extensive in one. Conclusion: Children with ALL in CR3 receiving HSCT are extremely high risk for relapse and transplant related mortality. These children have already relapsed twice and demonstrated chemotherapy resistance and GV/L/GVHD plays a key role in leukemia eradication. Although, TRM is high in such patients and GVHD could potentially increase TRM, there are no survivors without GVHD and exploring means of inducing GVHD by reduction of immunosuppressive medications or other means of immunotherapy should be considered in these patients.
follow-up time was 175.5 days (range 19-1402 days). Kaplan-Meier estimates were used for engraftment, relapse, TRM, OS and RFS rates with all patients who expired before engraftment counted as engraftment failures. Patients were also stratified by risk status. Results are summarized below. These results demonstrate that HSCT using unrelated PD UCB can be performed safely with outstanding results in pediatric patients with malignancies.

### Outcome Summary

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<th>Pct</th>
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<th>Plt</th>
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<td>64 days</td>
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<td>57±6%</td>
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<td>1-Yr</td>
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<td>OS</td>
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**361 SUPERIOR DISEASE-FREE SURVIVAL IN ACUTE MYELOGENOUS LEUKEMIA/MYELODYSPLASTIC SYNDROME RECEIVING REDUCED-INTENSITY ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM UNRELATED DONORS USING FLUDARABINE, BUSULFAN, AND TOTAL LYMPHOID IRRADIATION**

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Reduced-intensity stem cell transplantation (RIST) from unrelated donors (UD) is shown to be feasible treatment option for acute myelogenous leukemia/myelodysplastic syndrome (AML/MDS). Although morbidity and mortality from graft-versus-host disease (GVHD) may be still significant, transplant from UD may carry more potent graft-versus-leukemia (GVL) effect.

**Patients and Method:** A total of 36 patients (median age: 59 years old, range: 2-69) with AML/MDS were transplanted with RIST using related and unrelated donors. Patients were conditioned with fludarabine (125mg/m²), intravenous busulfan (6.4mg/kg), and total lymphoid irradiation (2-4Gy) (Flu/Bu/TLI). Tacrolimus and methotrexate were given as prophylaxis for GVHD. Twenty patients underwent RIST in complete remission (CR), and remaining 16 patients in non-CR. Related donors (RD) were used in 16 patients (8 in CR and 8 in non-CR at transplantation), and UD in 20 patients (12 were in CR and 8 in non-CR at transplantation).

**Results:** The median follow-up of survivors was 971 days (range: 109-1489), while 14 patients relapsed between 16 and 794 days (median 181 days). Overall survival (OS) and disease-free survival (DFS) at 2 years after RIST were 29.5% and 28.5%, respectively. The incidence of acute GVHD was relatively low (grade 0: 58%, grade 1: 19%, grade 2: 14%; grade 3-4: 8%). A survival advantage was seen for UD compared to RD (DFS at 2 years: 42% versus 23%, log-rank P = 0.0448). The relapse rate after RIST from RD was 71%, while from UD was 23%. The following factors were analyzed by univariate and multivariate analyses: age, sex, disease status at transplantation, source of stem cells (peripheral blood or bone marrow), RD or UD, number of CD34 positive cells transplanted, and acute GVHD. In univariate analysis, RD, non-CR at transplant, and low cell doses transplanted (UD) were identified as independent risk factors for DFS. Complete donor chimerism was achieved more consistently by day 100 in transplants from UD than from RD (P = 0.044).

**Conclusion:** Our observations suggest that RIST using Flu/Bu/TLI from UD is a feasible transplant option for AML/MDS patients, with possibly more potent GVL effect than using RD through early achievement of complete donor chimerism.

### 362 SUPERIOR EFS AND REDUCED TRM IN PATIENTS WITH INT-2 AND HIGH RISK MDS AND SECONDARY AML AFTER INITIAL CYTOREDUCTION WITH 5-AZA CYTIDINE

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Optimized preparative regimens and supportive care have allowed more MDS patients access to potentially curative stem cell transplantation. Early relapse accounts for up to 30% of advanced MDS. Leukemia induction chemotherapy prior to transplant reduces relapse incidence but with increased TRM. 5-Aza (5Aza) in advanced MDS may delay disease progression to AML, has a significant response, reduces marrow blast counts, often within the first 2-4 cycles, and is well tolerated. We examined the use of pre-transplant cytoduction with 5Aza in Int-2 or High risk MDS and secondary AML. Patients received at least 4 cycles of 5Aza. Patients with improving marrow blast counts continued on 5Aza to best response, those with greater than 20% blasts were treated with FLAG(n = 7), and 5Aza patients with progressive blast counts crossed over to FLAG(n = 5). Patients achieving CR/VGPR proceeded to transplant. 22 patients (median age 49 range 16-68) were followed from the initiation of treatment. With a median follow up of 235 days (range 36 to 1435), EFS of both 5Aza and FLAG treated patients was comparable (MS not yet reached) in contrast to shorter EFS of 5Aza patients crossing over to FLAG (MS 18 mo). Tests of equality over groups are not significant (Log-Rank p = 0.1652), although data suggests better early EFS in the 5Aza alone group. Of the initial 22 patients, 17 underwent allogeneic transplant (median age 46, range 16-62). The remainder were ineligible due to refractory disease, infection or comorbidities. Patients received targeted busulfan-based preparative regimens; 9 received MDI and 8 MUD transplant. With median follow up of >250 days(range 24-1304), EFS of the 5Aza group is superior to the FLAG group (MS not yet reached); both are far superior to the 5Aza to FLAG group (MS 7 mo; Log-Rank p = 0.0448). All patients receiving chemotherapy had a higher rate of early TRM compared with those receiving 5Aza alone. It is unclear if the inferior EFS of the 5Aza to FLAG group is due to higher TRM or identifies patients at higher risk for early relapse. While these cohorts are small, they represent the longest continuing follow up of patients treated with this strategy, and their survival compares very favorably with historical EFS for MDS. These early results suggest 5Aza as initial cytoductive therapy before transplantation is a strategy worth pursuing in planned larger multicenter trials to confirm these promising outcomes.

### 363 ADULT PATIENTS WITH MALIGNANCIES TRANSPLANTED WITH PLASMA DEPLETED CORD BLOOD (PD CB) – A RETROSPECTIVE AU-DITED ANALYSIS OF 68 PATIENTS

Nademanee, A.1, Graham, M.2, Ballen, K.3, Tan, A.M.4, Roenthal, J.1, Karanes, C.1, Eames, G.5, Tan, P.6, Jaing, T.-H.7

Optimized preparative regimens and supportive care have allowed more MDS patients access to potentially curative stem cell transplantation. Early relapse accounts for up to 30% of advanced MDS. Leukemia induction chemotherapy prior to transplant reduces relapse incidence but with increased TRM. 5-Aza (5Aza) in advanced MDS may delay disease progression to AML, has a significant response, reduces marrow blast counts, often within the first 2-4 cycles, and is well tolerated. We examined the use of pre-transplant cytoduction with 5Aza in Int-2 or High risk MDS and secondary AML. Patients received at least 4 cycles of 5Aza. Patients with improving marrow blast counts continued on 5Aza to best response(n = 10), those with greater than 20% blasts were treated with FLAG(n = 7), and 5Aza patients with progressive blast counts crossed over to FLAG(n = 5). Patients achieving CR/VGPR proceeded to transplant. 22 patients (median age 49 range 16-68) were followed from the initiation of treatment. With a median follow up of 235 days (range 36 to 1435), EFS of both 5Aza and FLAG treated patients was comparable (MS not yet reached) in contrast to shorter EFS of 5Aza patients crossing over to FLAG (MS 18 mo). Tests of equality over groups are not significant (Log-Rank p = 0.1652), although data suggests better early EFS in the 5Aza alone group. Of the initial 22 patients, 17 underwent allogeneic transplant (median age 46, range 16-62). The remainder were ineligible due to refractory disease, infection or comorbidities. Patients received targeted busulfan-based preparative regimens; 9 received MDI and 8 MUD transplant. With median follow up of >250 days(range 24-1304), EFS of the 5Aza group is superior to the FLAG group (MS not yet reached); both are far superior to the 5Aza to FLAG group (MS 7 mo; Log-Rank p = 0.0448). All patients receiving chemotherapy had a higher rate of early TRM compared with those receiving 5Aza alone. It is unclear if the inferior EFS of the 5Aza to FLAG group is due to higher TRM or identifies patients at higher risk for early relapse. While these cohorts are small, they represent the longest continuing follow up of patients treated with this strategy, and their survival compares very favorably with historical EFS for MDS. These early results suggest 5Aza as initial cytoductive therapy before transplantation is a strategy worth pursuing in planned larger multicenter trials to confirm these promising outcomes.