Autologous Transplantation for Hodgkin disease: A Tale of Two Eras

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Purpose: We evaluated outcomes for pediatric patients who underwent autologous hematopoietic stem-cell transplantation (AH SCT) for refractory or recurrent Hodgkin Disease (HD) to identify factors that contribute to the success or failure of their treatment.

Patients and Methods: From 1988 to 2012, 89 patients <21 years with relapsed or refractory HD underwent high-dose therapy followed by AH SCT according to one of several autologous transplantation protocols at Stanford University Medical Center (Stanford, CA). Pretreatment factors were analyzed by univariate and multivariate analysis for prognostic significance for 5-year overall survival (5 yr OS).

Results: The majority of the patients received a BCNU, etoposide, and cyclophosphamide conditioning regimen. The 5 yr OS in these patients was greater than that of recipients of either other chemotherapy-only preparative (e.g. CCNU, etoposide, cyclophosphamide or gemcitabine, vinorelbine, etoposide, cyclophosphamide) or radiation-containing regimens (75%, 61%, 50% respectively; P = .0057). AH SCT at or before second relapse resulted in better 5 yr OS than AH SCT later in the disease course (73% v 51%, P = .4). Patients who underwent AH SCT in 2002 or later had significantly better OS than those who underwent transplantation between 1988 and 2001 (80% v 65%; P = .07). Those in the earlier era were almost twice as likely to die within 5 years (risk ratio 1.97). This improvement in outcome is present even among patients who received BCNU containing conditioning (82% 5 yr OS 2002-2012 vs. 71% 5 yr OS 1988-2001, P = .21, risk ratio 1.89). 5 yr OS correlated most strongly with the era of transplantation. Most of the difference in outcome was attributable to decreased mortality in the peri-transplant period.

Conclusion: Approximately three-fourths of children who underwent AH SCT for their recurrent or refractory HD can be successfully treated with current therapy, confirming the continued efficacy of this approach. Analyses of results by treatment era suggest that supportive care during the peri-transplant period has improved outcomes. The BCNU, etoposide, and cyclophosphamide regimen was at least as effective as BEAM, and had greater OS than many published reports about outcomes using BEAM. Since outcome was related to disease status, pediatric patients should undergo AH SCT prior to second relapse.

Donor Lymphocyte Infusions in Pediatric Patients with Malignant and Non-Malignant Diseases After Allogeneic Bone Marrow Transplantation: A Single Center Experience

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Donor lymphocyte infusions (DLI) are used after allogeneic bone marrow transplantation (allo BMT) to treat and prevent relapse in patients with leukemia, to prevent graft rejection for non-malignant diseases, and to treat post-transplant lymphoproliferative disorder or viral infections. The data in children, particularly in non-malignant diseases, are limited and based on case reports and small series. We describe our experience in using DLI in pediatric patients with both malignant and non-malignant diseases after allo BMT over a 3-year period.

From November 2009 to October 2012, 11 pediatric patients, median age 9.5 years (range, 1.5-18.5 years), were treated with 22 doses of DLI. Median follow-up duration after DLI was 7 months (range, 2-32 months).

Six patients had hematological malignancies (3 – acute lymphoblastic leukemia, 2 – acute myeloid leukemia, 1 – chronic myeloid leukemia (CML)). DLI was given after salvage chemotherapy (5 children) to treat relapse and achieve remission status or to prevent relapse without previous chemotherapy (1 patient). Median time between BMT and DLI was 7 months (range, 4-18 months). Median CD3-T-cell dose of DLI in patients with acute leukemia was 5x10^7/kg (range, 1-10); a child with CML received 5 DLIs in escalating cell doses. Four of six patients had DLI from matched unrelated donors, and developed severe multisystemic graft versus host disease (GVHD).

Five children with non-malignant diseases (2 – thalassemia major, 2 – metabolic diseases, 1 – Immunodeficiency) had progressively decreasing chimerism and received DLI to prevent graft rejection. DLI was given 8 months (median; range, 2-9 months) after BMT. Median dose was 1x10^7/kg (range, 0.1-5). All patients had matched family donors (MFD). In 4/5 children, DLI prevented full rejection. In 2/5 children, stable mixed chimerism (25-35%) was enough to induce full remission of their basic disease. All were alive at the end of follow-up; none had GVHD.

Based on this experience, DLI achieved an excellent response for the patient with CML; but was not effective for treatment of full relapse in children with acute leukemia, and resulted in a high incidence of severe multisystemic GVHD. DLI could be an effective and safe method to prevent graft failure in children with non-malignant diseases after MFD. The absence of GVHD in this group is most likely due to family donors and reduced cell dose. Prospective studies of DLI in children are needed.

Bone Marrow Failure: Congenital Amegakaryocytic Thrombocytopenia - A Case Report of Successful Matched Unrelated Bone Marrow Transplantation in Pediatric Twins

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Congenital Amegakaryocytic Thrombocytopenia (CAMT) is a rare inherited autosomal recessive bone marrow failure disorder that presents with thrombocytopenia and absence of megakaryocytes. Bleeding/bruising is typically recognized on day 1 of life or at least within the first month, with risk of life threatening hemorrhage, requiring platelet transfusions
and progression to bone marrow failure and leukemic transformation later in life. Diagnosis is confirmed by the MPL gene testing. Allogeneic stem cell transplantation remains the only curative therapy. Due to its rarity, there are few published reports with variable conditioning regimens in the allogeneic setting.

We report two female identical twin siblings with thrombocytopenia at birth (11,000 and 9,000 respectively) and subsequent work up for persistent low platelets revealed heterozygous R102P missense mutation on exon 3 of MPL gene. No phenotypic abnormalities noted and Fanconi anemia testing was negative. One of them progressed to aplastic anemia (bone marrow cellularity< 30%, no clonal abnormality) and received conditioning with Cytoxan 50mg/kg x 4 days, reduced dose of TBI at 200cGy x 1 and Campath 3mg/kg x 4 days followed by transplant with 10/10 allele matched, unrelated, CMV + donor bone marrow. Tacrolimus alone was used for GVHD prophylaxis. Sister received myeloablative conditioning using once a day Busulfan for 4 days based on pharmacokinetics, Cytoxan 50mg/kg x 4 days, Campath 5mg/kg x 3 days followed by a transplant with the same unrelated bone marrow donor. Tacrolimus and mini methotrexate were given on days +1, +3, +6, +11. Both sisters tolerated the transplant with minimal toxicity, durable engraftment, and no acute or chronic GVHD. The first twin is approximately 1.5 years post BMT and the second is past day 100.

For matched unrelated donor transplant, the conditioning regimen used may be variable based on patients’ clinical presentation, bone marrow cellularity and presence of comorbidities.

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**Assessment of Iron Overload in Pediatric Patients With Thalassemia Major During One Year Follow-Up After Hematopoietic Stem Cell Transplantation Using T2 MRI Technique**

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**Background:** Iron overload especially in heart and liver cause serious complications for patients with thalassemia major (TM) including cardiomyopathy which is the main cause of death in TM patients. Using non-invasive methods for follow-up, MRI based methods like T2 MRI technique has been recently much more considered. This study investigates the changes in iron overload in TM patients before and after hematopoietic stem cell transplantation (HSCT) using T2 MRI technique.

**Methods:** Patients with TM who were candidate for HSCT enrolled. Cardiac and hepatic T2 values were measured three times during the treatment; one before HSCT, one six months later and the other one 12 months after HSCT. These values were compared to each other to determine how degree of iron overload changes during one year follow-up.

**Results:** Twenty-eight patients including 19 boys and 9 girls with mean age 7.27years (range: 3.5–13) were included. The mean± SD for cardiac T2 values before and after HSCT (6 and 12 months) were 18.00±7.13, 18.77±8.25 and 21.72±7.80 respectively. These numbers for hepatic T2 values were 5.11±4.03, 3.83±2.48 and 3.56±2.69 respectively. While the differences between cardiac T2 values during one year follow-up after HSCT were not statistically significant (P-value=0.19), hepatic T2 values have decreased significantly (P-value=0.001) meaning that although cardiac iron overload has not changed dramatically, hepatic iron overload is getting worse even one year after HSCT.

**Conclusion:** Using T2 MRI for measuring iron overload in TM patients shows that despite of receiving chelation therapy or phlebotomy after HSCT, hepatic iron overload is still getting worse in TM patients whereas cardiac iron overload is the same as before transplantation. It seems that for better understanding of liver iron overload, follow-up should be continued for years later.

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**Immune Reconstitution & Vaccine Response After Pediatric Allo-HSCT**

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**Background:** Transfer of donor immunity for vaccine preventable diseases in allo-HSCT is limited, requiring re-vaccination after HSCT. The CDC 2009 guidelines introduced changes, including earlier vaccination post-HSCT with a uniform vaccination strategy irrespective of transplant variables. The CDC guidelines acknowledge vaccination response varies, but significant knowledge gaps exist regarding factors affecting immune recovery and response to vaccination post-HSCT. The objective of this study is to describe predictors of immune recovery and adequate response to vaccination 1 year post-HSCT.

**Methods:** We conducted a retrospective chart review of all pediatric allo-HSCT patients transplanted between July 1, 2007 through June 30, 2012 who survived >1 year post-transplant without relapse (N=27). For evaluation of vaccine response, 8 patients were excluded (5 with incomplete data/refused vaccines, 2 with cGVHD, 1 receiving IVIG). Adequate response to vaccination was defined as a > 4-fold increase in tetanus titers >1 month after vaccination. Wilcoxon Rank-Sum Exact test and Kruskall-Wallis tests were used to analyze CD4, CD8, and CD19 counts with a type 1 error rate fixed at 0.05. Exact conditional logistic regression was utilized to analyze adequate vaccination response 1 year post-HSCT.

**Results:** Overall, a statistically significant increase in median CD4, CD8, and CD19 counts was seen from 6 to 12 months post-HSCT (P = <0.0001, 0.005, 0.004). Patients with aGVHD or cGVHD, however, lacked a significant increase in cell counts. Among graft sources, CBU recipients had the highest median cell counts. Among preparative regimens, patients with RIC had the lowest median cell counts. Only 36% of patients had adequate vaccination response at 1 yr post-HSCT. For the remaining evaluative patients, 88% required one and 12% required two additional re-vaccination attempts. None of the variables tested (graft source, preparative regimen, disease status, ATG/alemtuzumab, GVHD prophylaxis, cell counts, GVHD) were statistically significant in predicting adequate vaccine response.

**Conclusions:** There was no association between predictors of immune recovery or transplant variables and vaccination response in this study. A uniform vaccination strategy is unlikely to provide protective antibodies for many post-HSCT patients and should be evaluated in larger studies.