A scoring system predicting outcome after unrelated donor stem cell transplantation in primary refractory acute myeloid leukemia

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Conclusion: Our results indicate an increased risk of acute GvHD in association with DPB1 mismatch regardless of the TCE classification. TCE classification did not correlate with any transplant outcome considered in our cohort. This analysis does not support the clinical relevance of ranking DPB1 mismatches based on the TCE algorithm.

195

A SCORING SYSTEM PREDICTING OUTCOME AFTER UNRELATED DONOR STEM CELL TRANSPLANTATION IN PRIMARY REFRACTORY ACUTE MYELOID LEUKEMIA

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Treatment options for adults with primary refractory AML (PREF AML) are extremely limited. Whilst sibling allogeneic stem cell transplantation can result in long term survival most patients lack a matched family donor and are destined to die of refractory disease. Greater availability of unrelated donors and improvements in supportive care have increased the proportion of patients with PREF AML in whom allografting is technically feasible but the outcome of unrelated donor transplantation in this population has not been extensively studied. We therefore analysed overall survival in 168 patients with PREF AML who underwent unrelated donor transplantation between 1994 and 2006 with a median follow-up of 59 months (15-172). 80 patients received three or more courses of induction chemotherapy. The median percentage of bone marrow (BM) blasts at transplant was 39%. The 5-year overall survival for the whole group was 22%. In multivariate analysis, fewer than three courses of induction chemotherapy, a lower percentage of BM blasts at transplant and patient CMV seropositivity were associated with improved survival. We used the prognostic factors identified in multivariate analysis to develop a scoring system. This allowed the delineation of four prognostic groups with survival rates ranging between 44 ± 11% and 0%. This study demonstrates an important role for unrelated donor transplantation in the management of selected patients with PREF AML and confirms the importance of initiating an urgent unrelated donor search in patients with no matched sibling donor who fail to respond to induction chemotherapy. Pre-transplant factors allow the identification of patients with PREF AML who are likely to benefit from unrelated donor transplantation.

196

HLA DISPARITY AND RAPID IMMUNE RECONSTITUTION DO NOT OVERCOME PROPENSITY TO RELAPSE IN PATIENTS UNDERGOING HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) WITH PERSISTENT DISEASE AT THE TIME OF TRANSPLANT

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While increasing HLA disparity is known to be associated with increased risk of significant graft versus host disease (GVHD), there is less data as to whether increasing HLA disparity is correlated with stronger, clinically significant graft versus leukemia effects. We examined a group of patients with acute leukemia undergoing haploidentical HSCT to assess whether 1) there was a marked difference in relapse rates based on the degree of HLA mismatch and 2) if early recovery of donor lymphoid subpopulations was associated with less relapse after HLA mismatched HSCT. Thirty-four adult patients with AML (24) and ALL (10) underwent haploidentical HSCT between 2005 and 2009 using a 2 step process which separates the infusion of the lymphoid and myeloid portions of the graft while attempting to render the lymphocytes tolerant utilizing cyclophosphamide. The patients received 2 x10e8/kg donor CD3 cells (DLI) after conditioning with either TBI 12 Gy (N = 24) or fludarabine 30 mg/m2 × 4, thiotepa 5 mg/m2 × 3, and TBI 2 Gy (N = 10). Two days after the DLI, all patients received cyclophosphamide (CY) 60 mg/kg × 2 followed by a CD 34 selected donor product. The TBI based regimen was given to 80% of patients with ALL and 56% with AML. We examined relapse rates based on the number of antigen mismatches at A, B, Cw, and DRB1 in the GVH direction. There were no discernable differences based on degree of HLA disparity with even the most haplodisparate group exhibiting high rates of relapse when disease was present at HSCT. In contrast, the presence of active leukemia at the time of HSCT had far more impact on subsequent relapse rates (see Table).

Table 1. Outcomes Based on Degree of HLA Disparity

		4 Antigen Mismatch	3 Antigen Mismatch	2 Antigen Mismatch	1 Antigen Mismatch
	Number of Patients	Relapsed/ Total	Relapsed/ Total	Relapsed/ Total	Relapsed/ Total
Active Disease at HSCT	17 (50%)	10/12 (83%)	2/2 (100%)	3/3 (100%)	N/A
CR at HSCT	17 (50%)	3/9 (33%)	1/7 (14%)	N/A	0/1 (0%)
Total		13/21 (62%)	3/9 (33%)	3/3 (100%)	0/1 (0%)

We also examined the impact of immune recovery on relapse. Absolute numbers of NK, and CD4 and CD8 T cells were examined in the first 4 months post HSCT. T cell, MNC, and total chimerism was greater than 99% donor-derived at the time of the assessment. For patients who did or did not relapse post HSCT the median numbers of lymphoid subsets (cells/uL) were: NK 165 (77-700) vs 209 (77-660), CD4 105 (18-245) vs 98 (10-403), and CD8 82 (9-1039) vs 176 (2-2380) respectively. In this small series of patients treated with the 2 step transplant method, relapse was associated more with the presence of disease at HSCT than with any discernable trend in degree of HLA disparity or early immunologic recovery. Other approaches to treat resistant leukemia are required to substantially improve disease free survival in these high risk patients.

197

ANTI-HLA ANTIBODIES PREDICT GRAFT FAILURE, TIME TO ENGRAFTMENT AND UMBILICAL CORD UNIT DOMINANCE IN DOUBLE UMBILICAL CORD BLOOD TRANSPLANTATION

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Anti-HLA antibodies (HLA-Ab) predict graft failure in unrelated donor and single umbilical cord blood (UCB) transplantation. We measured HLA-Ab in double UCB transplantation (DUCBT) with the hypothesis that HLA-Ab would predict time to engraftment, graft failure and UCB unit dominance.

Methods: 73 patients with banked pre-transplant sera who underwent DUCBT using 4/6 or better allelic HLA-matched UCB units (2004 -2008) were studied. Labscreen (One Lambda Inc.) was used to capture class I/II HLA-Ab and the Luminex100 IS system was used to detect fluorescent tagged binding of human IgG. Visual software was used to normalize results and to determine the presence of mixed class I/II HLA-Ab. Positive samples were tested using single antigen-coated microbeads. Beads with a 1000 mean fluorescent intensity above baseline were considered positive. Chimerism was measured using STR typing of informative alleles. Graft failure was defined as the absence of neutrophil engraftment 42 days from DUCBT or loss of UCB chimerism by day 100 without malignant relapse. UCB dominance was defined as > 90% contribution to hematopoiesis by a single UCB unit at day 100.