Methods: The study cohort consists of 117 consecutive patients (28 matched siblings, 25 unrelated and 64 haplo) with 115 leukemia, 1 SAA, and 1 NHL. The median age is 20 years (3-62). Conditioning regimens: 1) Ara-C+BUCY (n = 14); 2) Ara-C+ BUFlu (n = 12). In addition, Haplo and URD received either 3) Ara-C+ BUCY +ATG (n = 54) or, 4) Ara-C+BUFlu+ATG. (n = 32) followed by unmanipulated G-CSF mobilized bone marrow and/or peripheral blood (G-BMPB or G-PB). 5 patients used other regimen. GVHD prophylaxis: CSA, MMF and short-term MTX. Multiple linear regression models were used for cost analysis. Variables considered were: transplant type (Sibling vs. URD vs. Haplo), quality of life (QOL), D/R sex match, patient age by decade, comorbidity, diagnoses, disease status pre-transplant, conditioning regimen, graft type, MNC, $CD34^+$cells, ANC and platelet engraftment, AGVHD and death.
Results: The median follow-up was 603 days (range 62 -1134). Clinical outcomes are shown in the following table.

Table 1. Clinical Outcomes after transplantation

	Sibling	URD	Haplo	P
TRM 100 day	0 (0-0)%	9 (2-24)%	5 (1-12)%	0.0634
TRM 1 year	12 (3-27)%	15 (4-32)%	14 (7-24)%	0.9488
Relapse 100 day	11 (3-25)%	4 (0-16)%	3 (1-10)%	0.4640
Relapse 1 year	23 (10-40)%	19 (9-41)%	9 (3-18)%	0.2187
DFS 100 day	89 (70-96)%	87 (65-96)%	92 (82-97)%	0.7817
DFS 1 year	65 (43-80)%	67 (37-84)%	77 (63-86)%	0.4721
Survival 100 day	96 (77-99)%	91 (69-98)%	94 (84-98)%	0.7430
Survival 1 year	84 (63-94)%	78 (49-91)%	83 (70-90)%	0.8780

The overall median cost (range) within 100-day of transplant was 52,373USD (13,627 – 262,716). The mean cost (95% CI) of HLA matched sibling, URD and haplo was 59,015 USD (45,537-72,493), 61,970 USD (47,701-76,224) and 63,373 USD (54,463-72,284) (P = 0.8674), respectively. Multivariate cost analysis indicated that QOL ≤ 80, conditioning including Flu or Flu+ATG and acute GVHD 2-4 correlated with increased cost.
Conclusion: These data suggest that transplant type (Sibling vs. URD vs. Haplo) does not significantly effect on the clinical outcomes and 100-day cost of transplantation. Future studies with more patients and longer follow-up are warranted.

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TOTAL DONOR CHIMERISM IN THE DAY 21 BONE MARROW PREDICTS SUSTAINED DONOR NEUTROPHIL ENGRAFTMENT FOLLOWING DOUBLE UNIT CORD BLOOD TRANSPLANTATION (CBT)

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Delayed or failed engraftment is a concern after CBT, even when using double unit grafts. Therefore, we analyzed the ability of the day 21 bone marrow (BM) composition and percent donor chimerism to predict sustained donor neutrophil engraftment in 56 recipients of myeloablative double unit CBT. Patients (median age 29 years, range 2-64) were transplanted for hematological malignancies, predominantly acute leukemia. Units had infused cell doses of 2.7×10^7 TNC/kg/ 1.2×10^5 CD34+ cells/kg for the larger unit, and 1.9×10^7 TNC/kg/ 0.7×10^5 CD34+ cells/kg for the smaller unit, with a donor-recipient HLA-match of 6/6 (n3), 5/6 (n59), and 4/6 (n50). The cumulative incidence (CI) of neutrophil engraftment was 95% (95% confidence interval: 89-100), with 47 patients engrafting with 1 unit and 6 engrafting with 2. The percentage of total myeloid precursors in the day 21 BM aspirate (median 40%, range 0-87), and the percent cellularity in the day 21 BM biopsy (median 5%, range 0-80), were both associated with neutrophil engraftment (Table 1). However, the most critical predictor of engraftment was the percent total donor chimerism (unit#1 + unit#2, median 100%, range 65-100), regardless if 1 or 2 units were present (Table 1). Sustained engraftment was seen in 98% of the 41 patients who were 100% donor at day 21 with a median day to absolute neutrophil count (ANC) ≥ 0.5 of 22 days. By contrast, only 87% of the 15 patients < 100% total donor engrafted [median day to ANC ≥ 0.5 31 days with a relative risk (RR) 0.3, p = 0.001]. Patients who were < 90% donor had especially poor engraftment (Table 1). The association between total donor chimerism and engraftment was independent of the percentage of myeloid precursors or BM cellularity. In patients (n = 37) without engraftment by day 21, a sub-group of particular clinical concern, day 21 total donor chimerism was also significantly associated with subsequent engraftment success (p = 0.003). No patient demographic was associated with total donor chimerism, and the only significant graft characteristic was the infused CFU dose of the engrafting unit (p = 0.002). These findings demonstrate the critical importance of the day 21 BM total donor chimerism and are of practical significance in the care of double unit CBT recipients. Further, they give interesting insights into double unit biology and suggest that the hematopoietic potential of the engrafting unit underlies the ability to generate complete donor chimerism.

Table 1. Cumulative incidence (CI) of neutrophil engraftment and median day to ANC >0.5 according to day 21 bone marrow composition and chimerism (n = 56).

Day 21 BM Characteristic	CI Engraftment by BM Characteristic Sub-group (Day ANC ≥ 0.5) (RR , p value)			P Value for CI Comparison
% Total Myeloid Precursors in Aspirate (n=56)	**<10% (n=18)** 95% (27 days) (RR 0.44, p=0.017)	**10-50% (n=18)** 89% (27 days) (RR 0.47, p=0.028)	**>50% (n=20)** 100%(22 days) Reference	0.017
% Cellularity in Core (n=56)	**<5% (n=21)** 91% (30 days) (RR 0.39, p=0.005)	**5-9% (n=15)** 100% (27 days) (RR 0.83, p=0.596)	**>10% (n=20)** 95%(21 days) Reference	0.005
% Total Donor Chimerism (n=56)	**<90% (n=6)** 67% (38 days) (RR 0.16, p=0.001)	**90-99% (n=9)** 100% (29 days) (RR 0.42, p=0.026)	**100% (n=41)** 98% (22 days) Reference	0.001

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THE T-CELL EPITOPE (TCE) ALGORITHM FOR CLASSIFYING HLA-DPB1 MISMATCHES DOES NOT PREDICT CLINICAL OUTCOMES IN HSCT

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A number of reports suggested the relevance of HLA-DPB1 matching for the outcomes of allogeneic hematopoietic stem cell transplantation (HSCT). An algorithm for determining DPB1 mismatch permissiveness based on T-Cell Epitopes (TCE) has been proposed (Zino et al, Blood 2004). According to this algorithm, all DPB1 alleles are categorized in 3 (TCE3) or 4 (TCE4) groups based on antigenicity. Accordingly DPB1 mismatches are classified as permissive; non-permissive in GvHD; or non-permissive in HvG direction.

Objective: To determine whether TCE classification is associated with HSCT outcomes. The outcomes considered in this analysis are failure to engraft, acute GvHD, chronic GvHD, and overall survival.

Methods: We analyzed 144 unrelated donor (≥ 7/8 allele matches at A, B, C, DRB1) allogeneic transplants performed in our center between 1999-2009. HLA-DPB1 mismatches were assessed using both TCE3 and TCE4 versions of the algorithm. Recursive partitioning analysis with a log-rank splitting method was used to categorize TCE variables into groups that best predict each outcome. Cox proportional hazards analysis was used to identify prognostic factors for each outcome.

Results: Graft failure was significantly highest among recipient with permissive DPB1 mismatches (AHR 9.87, 95% CI 1.21-80.3, P = 0.03) compared to recipients of zero mismatched, GvHD non-permissive, and HvG nonpermissive DPB1 mismatched donors. Acute GvHD was significantly higher in all DPB1 mismatches regardless of TCE classification (AHR 1.93, 95% CI 1.11-3.34, P = 0.02) compared zero DPB1 mismatch. There was no significant association between TCE classification and chronic GvHD, or overall survival.

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.

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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.

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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.

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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.