determined using a commercially available sandwich-type enzyme linked immunosorbent assay kit.
Results: Mean serum KL-6 levels +/− standard deviation for BMT subjects with BOS, BMT subjects without BOS and healthy controls were 571.6 +/−350.5, 302.3 +/−87.3 and 209.1 +/−77.6 U/ml, respectively. The difference between BMT subjects with BOS and those without BOS was statistically significant (p = 0.003) as well as those with BOS and healthy controls (p = 0.001). There was no statistical difference between BMT subjects without BOS and healthy controls (p = .956).
Conclusions: KL-6 levels were significantly elevated in BMT subjects with BOS as compared those without BOS and healthy controls. KL-6 could serve as a diagnostic tool in detecting BOS in BMT recipients.

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PERIPHERAL BLOOD STEM CELL TRANSPLANTATION VERSUS BONE MARROW TRANSPLANTATION IN SEVERE APLASTIC ANEMIA

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Introduction: Severe Aplastic Anemia (SAA) is a rare disease and the outcome of these patients has improved with hematopoietic stem cell transplantation (HSCT). In patients who have an HLA-identical sibling donor, HSCT is the preferred treatment. This is a retrospectively study in patients who received bone marrow (BMT) or peripheral blood stem cell transplantation (PBSCT) and compared the differences in hematologic recovery, acute and chronic GVHD, relapse and disease free survival and overall survival in two groups.
Methods: Totally 173 patients with diagnosis of SAA between March 1991 and October 2010, received allogeneic hematopoietic stem cell transplantation from an HLA-identical sibling donor (167 patients) or HLA full matched other related donor (6 patients). Three patients exclude from study because received both bone marrow and peripheral blood. Median age in BMT group was 17 years (range 1 to 32 year) and in PBSCT was 23 years (range 2 to 50 year). All patients received the conditioning regimen containing cyclophosphamide and ATG as our center protocol and cyclosporine and methotrexate for graft-versus-host disease (GVHD) prophylaxis.
Result: The median of follow-up was 40 and 20.5 month in BMT and PBSCT group respectively. The median time to reach ANC $\geq$ 500/mm^3 and platelet $\geq$ 20000/μl in PBSCT group (11 and 17 days, respectively) was significantly lower than BMT group (16 and 19 days, respectively) (P < 0.001). In two groups there was no difference in the incidence of acute GVHD (p = 1.0). The cumulative incidence of chronic GVHD for those who survived more than 90 days was 10.2% in the BMT group, compared to 27% in the PBSCT group (p = 0.022). Relapse of disease occur in twelve (24%) patients among BMT recipients and in 8 (6.5%) patients of PBSCT recipients (p = 0.005). Disease-free survival at 1 year was 74% in the BMT group and 86% in the PBSCT group (p = 0.24) and Overall survival at 1 year was 82% in the BMT group and 89% in the PBSCT group (p = 0.8). Nine patients in BMT group and 19 patients in PBSCT group were dead.
Discussion: However it seems that bone marrow is preferred source for progenitor cell for SAA transplantation but this study results showed that there was no difference in overall survival and disease free survival in two groups. But engraftment was rapid in multi-transfused patients who undergoing PBSCT than BMT with significant differences.

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PHASE II TRIAL: THE COMBINATION OF TACROLIMUS, SIROLIMUS, AND RABBIT ANTI-THYMOCYTE GLOBULIN (THYMOGLOBULIN® THYMO) TO PREVENT ACUTE GRAFT-VS.-HOST DISEASE (AGVHD) IN PATIENTS RECEIVING UNRELATED HEMATOPOIETIC STEM CELL TRANSPLANTATION (UHSCT)

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Background: Acute graft versus host disease continues to affect approximately 60% of patients undergoing UHSCT, with significant mortality and morbidity.
Methods: We prospectively evaluated the efficacy of combining Thymo (4.5 mg/kg divided doses on days -1,-2, and -3), Tacrolimus and Sirolimus in preventing aGVHD. The cumulative incidence rate at 100 days of grade II-IV aGVHD was calculated using death without grade II-IV aGVHD as competing risk. The median time to relapse, defined as time from BMT to the event of relapse or death due to relapse, was reported using KM method. The proportions of relapse, non-relapse mortality, cGVHD, and incidence of infections were reported with the Wilson's 95% Confidence Interval (in table below).
Results: Between August 2008 and August of 2010, 45 patients (pts) were enrolled, with median age of 53(20-70) years. The Median follow-up time is 10.5 months (1.3-26.5). There were 20 AML, 11 MDS, 4 ALL, 2 CML, 1 CLL, 3 Myelofibrosis, 2 multiple myeloma, 2 NHL pts. Preparative regimens included Bu/Flu (29), Bu/Flu-TBI (9), VP16/TBI (3), R-BEAM (1), and Flu/MEL-TBI (3). All pts received peripheral blood stem cells mobilized with G-CSF. Median CD34+ dose was 7.31x10^6 /kg (1.9-18.6). Twenty pts received 8/8 and 25 received 7/8 HLA matched grafts respectively. All patients' engrafted, with median day of 12 (9-18). Sixteen deaths occurred throughout the entire follow up period, due to: relapse (4), aGVHD (2), cGVHD (3), sinusoidal obstruction syndrome (SOS) (1), bleeding (1), multi organ failure (2), sepsis (2) and pneumonia (1). Eight patients experienced disease relapse. Twelve patients had non-relapse mortality.

Thirteen pts developed aGVHD, 7 grade I, 3 grade II, 2 grade III, and 1 grade IV. The cumulative incidence rate for grade II-IV aGVHD at 100 days is 0.13 (0.053, 0.250); the cumulative incidence rate of the competing event death without grade II-IV aGVHD at day 100 is 0.13 (0.053, 0.250). Thirteen pts developed cGVHD.

There were 2 cases of thrombotic thrombocytopenic purpura (TTP) before day 100. 14 CMV by PCR, 9 EBV by PCR, 6 HSV stomatitis, 6 BK cystitis, 27 bacterial infection, 3 oral candidiasis, and 3 SOS. The median time to relapse was 18.38 months.

Table 1. Phase II Trial Clinical Outcomes

Clinical Outcome	Incidence	Confidence Interval
Cumulative Incidence of Grade II-IV aGVHD	13%	(0.05-0.25)
Cumulative incidence of death without grade II-IV aGVHD before day 100	13%	(0.05-0.250)
Overall non relapse mortality	26%	(0.16-0.41)
cGVHD	28%	(0.17-0.43)
Relapse	17%	(0.09-0.31)
TTP	4.4%	(0.03-0.2)
CMV PCR	31%	(0.19-0.45)
EBV PCR	20%	(0.1-0.33)
HSV stomatitis & BK cystitis*	13%	(0.06-0.26)
Bacterial infections	60%	(0.45-0.73)
Oral candidiasis	6.7%	(0.02-0.17)
SOS	6.7%	(0.02-0.17)

*This incidence is for each of the the two viral infections.

Conclusion: These early results suggest that the combination of Thymo, Tacrolimus and Sirolimus in pts undergoing UHSCT is well tolerated and is associated with a low rate and severity of acute GVHD. Six months follow up data will be presented at the meeting.

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EFFECT OF RELATED AND UNRELATED DONOR HAEMATOPOIETIC STEM-CELL TRANSPLANTATION ON OUTCOME IN ADULTS WITH HIGH RISK HEMATOLOGICAL DISEASE: AN INTENTION-TO-TREAT ANALYSIS OF 410 PATIENTS AT A SINGLE CENTER INSTITUTION

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Allogeneic stem cell transplantation (SCT) from an HLA-matched related (MRD) or unrelated donor (MUD) is a curative option for patients (pts) with high-risk hematological disease (HRHD). In the absence of a MRD/MUD, pts have been offered investigational SCT strategies such as umbilical cord blood (UCB) or family haploidentical SCT (HAPLO). In our Institution, all patients with HRHD are typed at entry; if a MRD donor is missing a MUD search is promptly activated. A HAPLO is offered to pts lacking an MRD or MUD in order to adequately treat HRHD in the appropriate time, according to clinical indications and ongoing protocols. Here we report the intention-to-treat (ITT) analysis of alternative donor transplantation at our Institution. Data were obtained from Institutional databases.

Between Jan-2004 and July-2010, 410pts (age 48y, range 15-76) received indication to SCT according to EBMT recommendations. 246pts were diagnosed for acute leukemia (AL, 60%). 155pts (46%) were transplanted in persistence of disease (PD).

89pts (22%) received a transplant from a MRD; 190pts (46%) activated a MUD search; 84pts (20% of total, 44% of MUD searching) received a MUD transplant; 42pts (10%-21%) a HAPLO due to lacking of a suitable MUD; 11pts (3%-6%) a UCB. 149pts received a HAPLO (36%, 107 up-front). 21pts died before SCT (5%), 37 (9%) are still searching for a suitable donor and a donor is under evaluation for 19pts (5%).

The median time from diagnosis to SCT was 165 days, from MUD search to SCT 103 days.

The overall survival (OS) analysis in ITT is 51% at 1 year, 39% at 3y, for pts transplanted in complete remission (CR) 74% and 57%, for pts transplanted in PD 29% and 21% ($p < 0.0001$). The OS according to donor source (MRD-MUD-HAPLO) is comparable ($p = ns$) in pts transplanted in CR.

In the AL setting the 1y OS/transplant related mortality (TRM)/relapse incidence (RI) is 51%-27%-40% respectively; for pts transplanted in CR 77%-20%-25%, for pts transplanted in PD 20%-41%-67%. The outcome analysis per donor source is comparable ($p = ns$) within CR setting, while there is a trend of lower RI and TRM in the HAPLO vs MRD in PD pts.

In ITT 81% of overall pts received a SCT. The outcome achieved for pts transplanted in CR is comparable within the major donor sources (MRD-MUD-HAPLO). This result confirm the need to offer to every candidate pts a transplant option in the appropriate time and support the use of alternative donors, particularly HAPLO, in absence of an available MRD or MUD.

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MINIMAL RESIDUAL DISEASE STATUS AT DAY +100 POST ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IS A POWERFUL PREDICTOR FOR POST-TRANSPLANT OUTCOME IN PATIENTS WITH HIGH RISK ACUTE LEUKEMIA

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Background and Objectives: Relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) is still a major cause for the failure in treatment. The application of multiparameter flow cytometry (MFC) for minimal residual disease (MRD) assessment in high risk patients with acute leukemia (AL) who undergoing allo-HSCT was little concerned. We retrospectively analyzed the serial results of MRD of 52 high risk patients with AL to evaluate the prognostic value of MRD pre and post transplantation.

Methods: 52 patients with a median age of 29 (13–55) years have been enrolled on this study. Diagnoses included AML (n = 27) and ALL (n = 25). The patients had been analyzed retrospectively the level of MRD pre-(day-30)and post-HSCT(day+30 and +100)using three color FCM with CD45/SSC gating and a comprehensive panel of monoclonal antibodies, at least one leukemia associated aberrant immunophenotype (LAIP) at diagnosis. According to the cut off value 0.1%, two groups were defined based on the level of patient's MRD level < (low level group) or > = (high level group) 0.1%.

Results: The median follow up were 23 (range 1-60) months. 1.MRD level declines significantly ($P = 0.03$) post transplant. 2. There were significantly difference between low level and high level group at day -30 (before transplant) with 3 years event free survival (EFS) and relapse free survival (RFS) (77.4% vs. 22.3%, $p = 0.007$ and 88.4% vs. 25.7%, $p = 0.001$ respectively). 3. Concerning about MRD at day +100 after transplant, the outcome was significantly better among patients with low level MRD group versus high group including 3 years EFS and RFS (79.5% vs. 9.5% and 89.5% vs.11.2%, both $p < 0.001$). And the cumulative incidence of relapse for two groups were 7.4% and 80.9% ($P < 0.05$) respectively. 4. The median time from first time with high level MRD detected to clinical relapse was 2.5 (range from 1 to 33) months in relapsed patients. 5. The patients with cGVHD had better 3 years OS and EFS than that without cGVHD (86.3% vs 12.1%, $p < 0.001$ and 65.3% vs.14.8%, $p < 0.001$ respectively). 6. Multivariate Cox regression analysis revealed that MRD on day +100 as well as chronic GVHD were independent parameters predictive for OS and EFS.

Conclusions: MRD monitoring pre- and post-transplant are important tools to predict the outcome of transplantation for patients with high risk AL. The MRD check point at day +100 should be considered crucial for subsequent therapeutic decisions after allogeneic transplantation.

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DEVELOPMENT OF ADJUVANT ANTIVIRAL IMMUNOTHERAPY AFTER CBT USING DENTRITIC CELL VACCINATIONS

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Purpose: Elicit potent CD8+ T cell responses by dentritic cell (DC) vaccination to reduce viral reactivations in children and adults after cord blood transplantation (CBT).

Background: Although CB grafts have multiple advantages over conventional stem cell grafts, relapses and viral re-activations remain serious obstacles in children undergoing CBT. New strategies are needed to increase early specific adaptive immune responses after CBT in order to establish full clearance of, and long-term immunological memory against viruses.

Improvement in the presentation of viral-antigens by vaccination with viral-antigen loaded DCs may induce mass expansion of antigen-specific cytotoxic T lymphocytes (CTLs) in vivo, and subsequently reduce the risk of disease caused by viral re-activation after CBT. In mice, cross-presentation is induces after antigen uptake by the Fc receptor (FcR). We aim to improve the elicitation of virus specific CTLs, by targeting FcR mediated antigen uptake by DCs.

Methods: Immature DCs (iDCs) differentiated from the human CD34 derived DC progenitor cells, and human CB derived (hDCs) were pulsed with opsonized and non-opsonized EBV secreting B-cell (B-95-8) homogenates, obstained by mechanic cell fragmentation. Uptake via FcRs was blocked by using human IgG Fc fragments or anti-CD16, -CD32 and -CD64 F(ab')2-fragments. The amount of cross-presentation was measured through cytokine production by an EBV specific CD8 T cell clone, both by Elispot IFN-y measurements and FACS analysis of intracellular cytokine and proteases production (IFN-y, TNF-a, granzyme B and perforin) and presence of the late endosomal marker (LAMP-1) on the cell surface.

Results: We show increased binding and uptake of EBV/B cell fragments when these fragments are targeted to Fc receptors for uptake by DCs. We have generated multiple CD8 T cell clones that are TCR specific tot the immunodominant EBV GLCTLVAML peptide (from the EBV lytic protein BMLF1 corresponding to residues 280–288). We are currently testing whether FcR targeting of EBV/B cell fragments to DCs improves the elicitation of potent CD*+ T cell responses.

Conclusion: Optimizing cross-presentation in CB derived DCs may be an important and effective tool in the development of adjuvant anti-viral immunotherapies after CBT to induce early potent anti-viral responses.