Oral Presentations

ALLOGENEIC TRANSPLANTS

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LONG-TERM OUTCOME OF METHOTREXATE-FREE GVHD PROPHYLAXIS USING SIROLIMUS AND TACROLIMUS IN MATCHED RELATED (MRD) AND UNRELATED DONOR (URD) PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (PBSCT)

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We report here our long-term results of sirolimus and tacrolimus without methotrexate (Mtx) after MRD and URD PBSCT. **Methods:** Transplanted subjects had HLA-A, B, C and DRβ1 matched MRD and URD donors. Conditioning consisted of cytoxan (1800 mg/m^2 x 2) and TBI (14 Gy, 7 fractions). Tacrolimus (serum conc. 5-10 ng/mL) and sirolimus (serum conc. 3-12 ng/mL) were given without Mtx as GVHD prophylaxis. G-CSF (5 μg/kg/day) was administered from day+12 until neutrophil engraftment if needed. **Results** 53 MRD and 30 URD recipients were transplanted between 7/2002 and 8/2005. The median number of stem cells infused was lower in MRD recipients (7.6 $\times 10^6$ vs. 10.2 $\times 10^6$ CD34$^+$ cells/kg, p<0.001), however, neutrophil engraftment was similar (14 vs. 13.5 days, p=0.2). Platelet engraftment to 20 $\times 10^6$/ml (12 vs. 12 days, p=0.13) and to 100 $\times 10^6$/ml (17.5 vs. 17 days, p=0.32) was similar in the two cohorts. The median time to hospital discharge was 19 days in both groups (p=0.95), with only 2 deaths (2.4%) prior to discharge. Transplant-related toxicity included acute lung injury (IPS/DAH, n=1, 1.2%), hepatic veno-occlusive disease (VOD, n=7, 8.4%) and thrombotic microangiopathy (TMA, n=6, 7.3%). The cumulative incidence of grade II-IV acute GVHD was 20.5%, and was not different between cohorts (18.9 vs. 23.3%, p=0.78). There were only 3 cases of grade III-IV acute GVHD (2 MRD, 1 URD). In a competing risk model (relapse/death as competing risk) the cumulative incidence of chronic GVHD was 52.4% and was not different between groups (50.9 vs. 53.3%, p=0.67). The median follow-up of all surviving patients is 32.8 months from transplantation. Non-relapse mortality at 30 and 100 days was 0% and 4.8%. Relapse-free survival for the entire group was 72.3% and 68.5% at 1 and 2 years (MRD 71.7% and 66.0%; URD 73.3% at both times, log rank p=0.5). Overall survival at 1 and 2 years is 77.1% and 72.2% (MRD 77.4% and 69.8%; URD 76.7% at both times, log-rank p=0.58). Causes of death include relapse(13), VOD(4), late pulmonary disease(3), GVHD(2), infection and organ failure(2). **Conclusions** We conclude that sirolimus in lieu of Mtx with tacrolimus for GVHD prophylaxis is associated with low transplant-related toxicity, low rates of acute GVHD and excellent outcomes. Moreover, MRD and URD outcomes appear to be equivalent, suggesting that the historical disparity in outcomes between MRD and URD transplantation can be abrogated with effective GVHD prophylaxis.

Summary of Major Clinical Endpoints

	Combined	MRD	URD	p
Engraftment (days)				
ANC > 500	14	14	13.5	0.2
Plt > 20 000	12	12	12	0.13
Plt > 100 000	18	17.5	17	0.32
1st Discharge	19	19	19	0.95
GVHD				
Acute Gr. II-IV	20.5%	18.9%	23.3%	0.78
Acute Gr. III-IV	3.6%	3.6%	3.3%	0.99
Chronic	52.4%	50.9%	53.3%	0.67
Survival				
30-day NRM	0	0	0	NA
100-day NRM	4.8%	5.7%	3.3%	
1-yr RFS	72.3%	71.7%	73.3%	0.5
2-yr RFS	68.5%	66.0%	73.3%	
1-yr OS	77.1%	77.4%	76.7%	0.58
2-yr OS	72.2%	69.8%	76.7%	

ANC = Absolute Neutrophil Count; Plt = Platelet; NRM = Non-Relapse Mortality; RFS = Relapse-Free Survival; OS = Overall Survival

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HIGH RECIPIENT CD4$^+$CD25^{HI} REGULATORY T-CELL LEVEL PRE-TRANSPLANT IS ASSOCIATED WITH REDUCED OVERALL SURVIVAL AFTER UNRELATED DONOR HEMATOPOYETIC STEM CELL TRANSPLANTATION

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CD4$^+$CD25^{hi} T-cells (T-regs) have been identified as a naturally occurring regulatory T-cell population. T-regs express FOXP3, produce anti-inflammatory cytokines such as TGFβ upon activation, and are essential to maintain tolerance. Their potential impact on the alloreactive phenomena and the outcome of HSCT in humans, however, remains controversial. We have analyzed the effect of pre-conditioning peripheral blood levels of CD4$^+$CD25^{hi} T-regs on the outcome of 89 adult patients undergoing HLA-identical (10/10) unrelated donor (UD)-HSCT. Allografts were T-cell depleted with Alemtuzumab, which has been described to preserve T-regs from depletion. The percentage of T-regs pre-transplant had no effect on transplant related mortality or the incidence of acute GVHD, but higher T-regs levels did associate with a higher risk or relapse (p=0.027) and the incidence of chronic GVHD (p=0.033). Overall, patients with a higher proportion of CD4$^+$CD25^{hi} T-cells had a reduced overall survival following UD-HSCT (30% vs 65%, median follow up 1013 days; p=0.002).

Although T-regs have been clearly identified by the expression of the transcription repressor factor FOXP3 in mice, FOXP3 expression in humans is not restricted to CD4$^+$CD25^{hi} T-cells. In a healthy donor control group (n=30), CD4$^+$CD25^{hi}-expression correlated well with both, FOXP3 mRNA-expression (r=0.649; p=0.001) and TGFβ production (r=0.912; p<0.001), as previously described for T-regs. In preconditioning patient samples, CD4$^+$CD25^{hi}-expression had also a strong correlation with TGFβ regulatory cytokine production (r=0.863; p<0.001), as well as an inverse correlation with TNFα expression (r=-0.458; p<0.001), in keeping with a true regulatory phenotype. FOXP3 mRNA-expression, however, correlated neither with the CD4$^+$CD25^{hi} T-regs phenotype (r=0.280; p=0.040), nor with TGFβ production (r=0.229; p=0.156), and appeared not be an accurate marker for regulatory T-cell function in this patient setting.

In summary, preconditioning patient percentage of T-regs may influence the outcome of UD-HSCT through their effect on alloresponses against the tumour and the host. Accurate identification of T-regs in these patients requires the analysis of their immunophenotype and expression of functional markers. FOXP3 expression, however, may not identify true regulatory T-cell function in patients undergoing UD-HSCT.

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ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN HIV-POSITIVE PATIENTS WITH MALIGNANT AND NON-MALIGNANT DISORDERS: A REPORT FROM THE CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH (CIBMTR)

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