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FLUDARABINE-BASED NON-MYELOABLATIVE STEM CELL TRANSPLANTATION IN A PATIENT WITH SICKLE CELL DISEASE AND RENAL FAILURE: CLINICAL OUTCOME AND PHARMACOKINETIC COMPARISON TO PATIENTS WITH NORMAL RENAL FUNCTION

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End-organ damage is common in adult patients with Sickle Cell Disease (SCD), therefore an effective non-myeloablative approach to allogeneic stem cell transplantation (SCT) would be ideal. Fludarabine is a component of most non-myeloablative conditioning regimens. Since 40% of the active metabolite, 2-fluoro-ara-A (F-Ara-A), is cleared by the kidneys, use in patients with renal insufficiency or renal failure is hazardous. We report the outcome of two adult SCD patients who underwent non-myeloablative SCT from their HLA-identical matched siblings on an NHLBI-sponsored clinical trial. Patient #1 is a 21 year-old male with normal renal function and patient #2 a 27 year old with dialysis-dependent end-stage renal disease. Conditioning consisted of Total Body Irradiation 200cGy followed by Fludarabine (Pt #1: 30 mg/m^2, Pt #2: 24 mg/m^2) Cyclophosphamide 500mg/m^2, both given over four days and Campath 1-H 100mg over 5 days. Mycophenolate Mofetil 2 grams/day was given for 100 days. Patient #1 and #2 received peripheral blood stem cell grafts containing 21×10^6 and 19×10^6 CD34$^+$ cells/kg, respectively. Patient #2 underwent 6 hours of conventional hemodialysis using an F200 dialyzer, 12 hours after each Fludarabine dose. Plasma samples from patient #2 and two additional non-SCD patients with normal renal function undergoing stem cell transplantation using the same chemotherapy preparative regimen were collected over 24 hours after doses 1 and 4 of Fludarabine. F-Ara-A was measured by a validated LC/MS/MS assay. Both SCD patients achieved full donor erythroid chimerism and stable mixed lymphoid and myeloid chimerism (donor CD15/CD3; Pt #1 89%/87% 14 months post-transplant, Pt #2 86%/45% 6 months post transplant). Neither patient developed graft vs host disease, neurological complications or any other SCD-related complications following transplantation. Both have normal blood counts and are on no immunosuppressive medications. F-Ara-A pharmacokinetic parameters obtained using non-compartmental analysis are given in the table. With a 20% dose reduction followed by intensive daily dialysis, we achieved Fludarabine levels that are nearly identical to that achieved in patients with normal renal function. This allowed for robust donor stem cell engraftment without Fludarabine-related toxicity. We conclude that non-myeloablative allogeneic SCT for adult patients with SCD is feasible, even in the setting of end-stage renal disease.

First Dose Fludarabine Pharmacokinetic Parameters

Patient with:	C_{max} (μ/L)	$t_{1/2}$ (h)	CL (L/h)	V_{ss} (L)	AUC_{last} (mg·h/L)
Renal Failure and SCD	**549**	**5.9**	**5.3***	**52**	**4093**
Normal Renal Function-1	**788**	**10.5**	**6.4**	**72.6**	**3972**
Normal Renal Function-2	**1170**	**9.2**	**6.4**	**59.6**	**4049**

*calculated from dialysis phase slope; **C_{max}** Maximum Concentration, **$t_{1/2}$** half life, **CL** clearance, **V_{ss}** Steady State Volume of Distribution, **AUC** Area under curve

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DONOR KILLER IG-LIKE RECEPTOR HAPLOTYPE IS ASSOCIATED WITH LOWER RELAPSE IN CHRONIC MYELOGENOUS LEUKEMIA PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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In allogeneic hematopoietic cell transplantation (HCT), donor natural killer (NK) cells can prevent leukemia relapse and prolong survival. NK alloreactivity has been shown to be influenced by the killer Ig-like receptor (KIR) repertoire of the donor and the HLA class I KIR ligand phenotype of the recipient. We sought to determine if more activating receptors in the donor KIR repertoire would influence the outcome of allogeneic transplant for hematologic malignancies. Comprising 50% of all haplotypes in the Caucasian population, KIR haplotype-A is a conserved haplotype with nearly no activating KIR. In contrast, haplotype-B comprises a variety of different haplotypes, most of which contain several activating KIR. Using data provided from the International Histocompatibility Working Group, we studied the donor KIR genotypes from 541 unrelated donor transplants and examined the impact of donor KIR haplotype on overall surivival (OS) and relapse, by segregating donor-recipient pairs into those in which the donor was homozygous for KIR haplotype A (AA) versus those in which the donor was heterozygous or homozygous for the B-haplotype. Models were adjusted for disease severity, HLA-mismatch, and patient age. There was no survival advantage to having a donor with a B haplotype compared to AA donors (HR 1.05, 95% CI 0.80-1.37, p=0.73). However, there was a significant effect of donor B haplotype on relapse, where the presence of a donor B haplotype (n=330) compared to donor AA (n=162) was associated with significantly lower hazard of relapse (HR=0.41, 95% CI 0.33-0.67, p<0.0001). The haplotype B effect on relapse was overwhelming strong in transplants for CML (n=189, HR=0.15, 95% CI 0.08-0.27, p<0.0001). There was no significant donor B-haplotype effect on relapse in AML (n=104, HR 0.80, 95% CI 0.40-1.63, p=0.54) or ALL (n=96, HR 0.76, 95% CI 0.30-1.95, p=0.57). There was no clear association between any specific activating KIR and decreased relapse, nor was there was an association between cumulative numbers of activating KIRs and decreased relapse. These results suggest that the association between haplotype B and decreased relapse in CML may be related to factors other than activating KIR present or associated with the B-haplotypes and absent in the A-haplotype. These results have implications for donor selection in patients with CML who are referred for allogeneic transplantation.

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ALLOGENEIC BLOOD AND MARROW TRANSPLANTATION IN THALASSEMIA MAJOR CLASS 3: AN EXPERIENCE OF IRAN

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Objective: Our aim for this study was to describe the outcome of blood and marrow transplantation in patients with class 3 Thalassemia major.

Methods: Since December 1992 till september 2006, fifty-two patients with Thalassemia class 3 received blood and marrow transplantation from their Human Leukocyte Antigen(HLA)-identical siblings. Thirty-two patients received bone marrow and twenty patients received peripheral blood stem cell transplantation. Conditioning regimen in 47 patients was Cyclophosphamide 40 mg/kg/day (from day–5 to -2) and Busulfan 3.5 mg/kg/day (from day –9 to -6) and in these patients Graft Versus Host Disease (GVHD) prophylaxis regimen was Cyclosporine.A (CY.A) 1.5mg/kg /day/IV (day–3), then 3mg/kg/day IV (days +7, +11), then 12.5 mg/kg/day/PO and Methotrexate 10mg/m^2 (day +1), 6mg/m^2 (days +3, +6). Conditioning regimen in 5 patients was Fludarabin 40 mg/m^2 (from –6 to –2) and Busulfan 4 mg/kg (from –5 to –2) and in this patients GVHD prophylaxis regimen was (CY.A) 3 mg/kg/day IV (days –3 and +7), then 12.5 mg/kg/day PO.

Results: Median age at time of transplantation was 8.5 years (age range: 1-26), Male/Female: 21/31.Median time of absolute