Successful Engraftment and Cure of Sickle Cell Disease after Co-transplantation of NiCord® (*Ex Vivo* Expanded UCB Progenitor Cells with Nicotinamide) and a Second Unmanipulated Cord Blood Unit after Myeloablative Chemotherapy in Children with Severe Sickle Cell Disease

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Background

- Patients with severe sickle cell disease (SCD) experience organ damage, poor quality of life and premature mortality
- Allogeneic hematopoietic stem cell transplant (HSCT) from a matched related bone marrow donor is the only established curative therapy to date
- Most patients in need of HSCT do not have matched related or unrelated donors
- Umbilical cord blood is easily available, and transplants (UCBT) using partially mismatched grafts are feasible, thus increasing access to transplant
- However, UCBT is associated with increased graft failure risk in patients with hemoglobinopathies: inadequate cell dose in the graft has been noted to be an important variable associated with graft failure
- NiCord® is an *ex vivo* expanded product made from a cord blood unit (CBU) using nicotinamide-based technology
- NiCord®, in combination with an unmanipulated CBU (pilot study at Duke University; *Horwitz et al JCI 124:7, 2014*) or as a standalone graft (Phase I/II multicenter study; *Horwitz et al. 2016 ASCO Annual Meeting*), has shown rapid and sustained engraftment in adults with high-risk hematologic malignancies

Hypothesis

Co-transplantation of NiCord® & an unmanipulated CBU will be safe and improve engraftment in patients with sickle cell disease undergoing myeloablative HSCT

Study Objectives

PRIMARY OBJECTIVES
- Assessment of the acute toxicity associated with the infusion of NiCord®, within 24 hours post-infusion
- Assessment of cumulative incidence of donor-derived neutrophil engraftment by day 42 following co-transplantation of NiCord® and unmanipulated cord blood grafts

SECONDARY OBJECTIVES
- Treatment related mortality at 180 days
- Event-free survival at 100 days
- Overall survival at 180 days

EXPLORATORY OBJECTIVES
- Donor chimerism
- Pace of neutrophil, platelet and immune recovery
- GvHD, regimen-related toxicity, infections

Phase I/II Study Design

ELIGIBILITY
- Age between 2-45 years old
- No available MRD or 8/8 unrelated adult donor
- High risk disease
  - Stroke, abnormal TCD or brain MRI/MRA
  - Recurrent acute chest syndromes
  - Recurrent vaso-occlusive crises
- Satisfactory organ function
- Negative anti-HLA antibody screens for donor HLA
- Grafts 4/6 matched or better with patient
- Minimum pre-freeze TNC dose requirement
  - NiCord® unit 1.8 x 10^7/kg
  - Unmanipulated unit 3.5 x 10^7/kg
- Autologous Bone Marrow back-up

CONDITIONING
- Myeloablative conditioning regimen
  - Hydroxyurea (day -35 until start of high dose chemotherapy)
  - Busulfan 1 mg/kg IV q 6 (days -9 to -6)
  - Cyclophosphamide 50 mg/kg/day (days -5 to -2)

+

- Equine ATG 30mg/kg//day (days -3 to -1) [N=3] (For the first 3 patients in the study)

OR

- Fludarabine 35 mg/m2/day (days -14 to -10) [N=6]

DOUBLE CORD CONFIGURATION:

NiCord®, Cryopreserved Product
Shipped to the transplant center ready for infusion

NiCord® Product Manufacturing

CliniMACS separation: Enrichment of CD133+ cells

CD133+ fraction	CD133 negative fraction
Cultured for 3 weeks with cytokines (TFS6) and Nicotinamide (Vit B3 derivative, NAD precursor, inhibits Sirtuin 1, type III NAD-dependent deacetylase)	T cell containing fraction, Cryopreserved until the day of transplantation

+

Unmanipulated CBU

Demographics & Transplant Outcomes

Pt	Age (yrs)	Indication	NiCord® Cultured Fraction INFUSED		Engraftment (day)		Maximum GvHD Acute / Chronic	GvHD at last F/U	Chimerism Day 7			Chimerism Last F/U			SCD Status: Transfusion Free	F/U (months) * = died
			Total cells x 10^7/kg	CD34+ x 10^5/kg	ANC >500	Platelet > 50			NiCord®	UM	Host	NiCord®	UM	Host		
1	12.9	VOC, Abn TCD	4.4	38.3	7	71	III	None	97	3	0	0	100	0	Yes	48
2	8.9	VOC, ACS	9.9	173	9	n/a		n/a*	90	0	10	0	0	100	n/a	1*
3	4	VOC, ACS	13.8	195	20	375	III/Extensive	None	100	0	0	0	100	0	Yes	44
4	16.9	VOC, ACS	5.1	65.7	6	55	II/Limited	None	97	0	3	100	0	0	Yes	39
5	11.8	VOC, ACS	7.3	127.1	7	57		None	100	0	0	11	89	0	Yes	36
6	3.4	VOC, ACS	7.3	88	7	33		None	87	0	13	0	100	0	Yes	12
7	16.9	VOC, ACS	4.4	93.7	7	47	IV/Extensive	Extensive*	84	0	16	0	100	0	n/a	8*
8	14.7	VOC, ACS	6.6	123.5	7	42	II	None; on IS	100	0	0	100	0	0	Yes	7
9	16.6	VOC, TIA, Abn MRA	2.6	44.9	8	n/a		None	73	0	27	80	20	0	Too early	0.7
Median	**12.9**		**6.6**	**93.7**	**7**	**55**										

Abbreviations: Abn = abnormal; F/U = Follow up; IS = immunosuppressive agents; UM = unmanipulated

Results

- N = 9; M:F 4:5
- Median age 12.9 years (3.3 – 16.9 yrs)
- HLA match of patient with:
  - NiCord® unit 4/6 (n=8); 5/6 (n=1)
  - UM unit 4/6 (n=6); 5/6 (n=3)
- Initial Engraftment noted in all 9 patients :
  - Median time to engraftment:
    - Neutrophils 7 days (range: 6-20 days)
    - Platelets 51 days (range: 31 -94 days)
  - 1 patient had secondary graft failure
- Acute GvHD II-IV: N=5
- Chronic extensive GvHD: N=2
- 2 patients died: 1 from infectious complications after second transplant (Pt #2); 1 from liver GvHD (Pt #7)
- Transfusion independence: 7 patients (1 patient too early)
- Hemoglobin profile (post-transplant): Normal in 7 patients
- Survival: 7/9 patients are alive at a median follow-up of 36 months (0.7 – 48 months)

Conclusions

- NiCord® appears to overcome the engraftment barriers of UCB in SCD patients in a myeloablative setting. Sustained donor cell engraftment was achieved in 8/9 patients, despite 4/6 matched UCB units and in 6 patients without ATG
- Rapid engraftment was achieved consistently with NiCord® approach, most of the patients engrafting within 7-8 days
- Patients consistently achieve transfusion independence and normal hemoglobin profile post-transplant
- Factors influencing one graft to dominate over another need further study
- None of the survivors have active GvHD at the last follow up. However, GvHD is a challenge and further optimization of this approach with strategies to further decrease GvHD is warranted
- NiCord® has the potential to increase access to curative transplantation for SCD patients by enabling the successful use of unrelated UCB donors