ABSTRACT PF728

Non-HLA Matched, Ex-Vivo Expanded Cord Blood Product Significantly Improves the Kinetics of Hematopoietic Recovery and Results in Excellent Survival in Patients Undergoing Cord Blood Transplantation

Filippo Milano[1], Emily Cox[1,2], Shelly Heimfeld[1,2], Irwin Bernstein[1], Frederick Appelbaum[1], Colleen Delaney[1,2]

[1]Clinical Research Division, Fred Hutchinson Cancer Research Center; [2]Nohla Therapeutics, Inc.

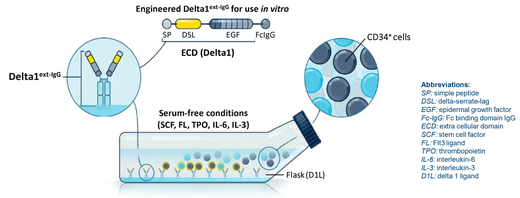
BACKGROUND

Allogeneic hematopoietic cell transplantation remains the only known curative approach for patients with high-risk leukemia; however, access is limited by donor availability. Umbilical cord blood (CB) has emerged as an important source of donor stem cells, particularly due to a decreased risk of graft-versus-host disease (GVHD) and potential improvement in graft versus leukemia effect. However, the low number of CD34+ cells in CB grafts can lead to delayed hematopoietic recovery, resulting in increased risk of morbidity and mortality post-transplant.

AIMS

With the goal of enhancing the kinetics of hematopoietic recovery and improving transplant outcomes, we developed methods to ex-vivo expand CB-derived hematopoietic stem/progenitor cells (HSPC) using an engineered Notch ligand to increase the absolute number of rapidly repopulating HSPC for clinical applications. The final expanded product (NLA101) is a cryopreserved non-HLA matched clinical product for use as a T-cell depleted, universal donor graft source available for immediate use.

NLA101 Expansion Process



METHODS

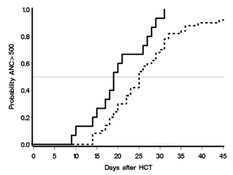
Between 2010 and 2012, 15 patients with hematologic malignancies were enrolled in a single center, Phase 2 trial to assess safety and feasibility of infusing NLA101 to augment myeloablative CB transplant (CBT). All patients received conditioning of fludarabine 75 mg/m^2; cyclophosphamide 120 mg/kg; and 13.2 Gy TBI. On transplant day, the unmanipulated CB unit(s) was infused first followed 4 hours later by infusion of NLA101. GVHD prophylaxis consisted of cyclosporine/MMF.

Hematopoietic recovery was analyzed using cumulative incidence (CI) rates to accommodate competing risks. Disease-free survival (DFS) and overall survival (OS) were analyzed using Kaplan-Meier estimates. Outcomes were compared to a concurrent control cohort of 50 patients enrolled on a standard of care cord blood transplant protocol who were treated identically except they did not receive any NLA101 cells. No significant differences between the two cohorts were found with respect to age, sex, weight, disease, and MRD status. We herein report long-term follow-up data from this study.

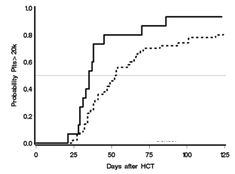
RESULTS

Fifteen patients, median age 21 years (range 5-45), being treated for ALL (n=8), AML (n=6) and MDS (n=1) were enrolled and included in this analysis. The median CD34+ and TNC cell doses of NLA101 were 5.3 (range 3.1-11.6) x10^6 cells/kg and 5.8 (range 2.2-10.9) x10^7 cells/kg, respectively. Median follow-up for the NLA101 + CBT group is 6.5 years and 7.9 years for the control cohort. Patient characteristics and clinical outcomes shown below are summarized in the table.

Neutrophil Recovery



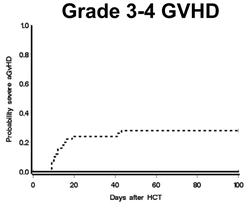
Platelet Recovery



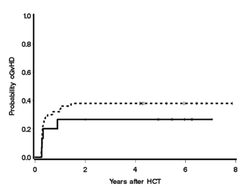
Time to neutrophil and platelet recovery was significantly improved over the control. CI at day 100 of neutrophil recovery was 100% vs. 94% (p=0.005), with a median time of 19 days (range 9-31) vs. 25 days (range 14-45) in the control. CI at day 100 of platelet recovery was 93% vs 74% (p=0.02), with a median time of 35 days (range 21-86) vs. 48 days (range 24-158) in the control.

No patients in the NLA101 group experienced severe grade 3-4 acute GVHD (100 days) vs. 29% in the control group. At 5 years, 27% of the NLA101 group had experienced chronic GVHD vs. 38% of the control group. Of the 13 evaluable patients in the NLA101 cohort, 9 patients (69%) were off immunosuppression therapy at 2 years post-CBT.

Severe Acute Grade 3-4 GVHD

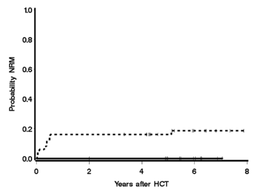


Chronic GVHD

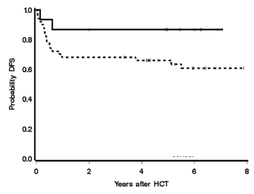


No patients in the NLA101 group experienced transplant related mortality (TRM) vs. 16% of the control group. Two of the 15 patients (13%) receiving NLA101 relapsed post-transplant and subsequently died. DFS and OS in the NLA101 group remained excellent at 5 years post-CBT at 86.6% vs. 66% for the control group.

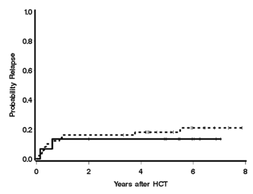
TRM



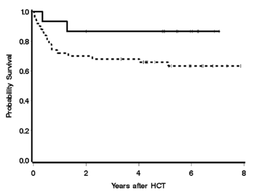
DFS



Relapse



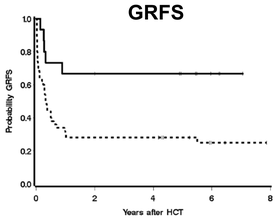
OS



CBT
NLA101 + CBT
Censored

The composite endpoint of GVHD/ Relapse-free Survival (GRFS) was analyzed to measure survival without ongoing morbidity, which represents ideal recovery after stem cell transplant. At 5 years GRFS for patients who received NLA101 was 67% vs. 28% in the control group.

GRFS



	NLA101 + CBT (n=15)	CBT (n=50)
Patient Characteristics	**No. (%)**	
Gender		
Male	8 (54)	25 (50)
Female	7 (46)	25 (50)
Age in years, median (range)	21 (5-45)	21 (0.6-43)
Weight in kilograms (range)	59 (23-89)	67 (8-109)
Diagnosis		
ALL	8 (53)	16 (32)
AML	6 (40)	24 (48)
MDS/CML	1 (7)	6 (12)
Other		4 (8)
CMV seropositive	11 (73)	31 (50)
Race		
Caucasian	4 (27)	21 (42)
Other	11 (73)	29 (58)
Follow-up in years, median (range)	6.5 (5.6-7.4)	7.9 (3.1-10.3)
CD34+ cell dose x 10^6 cells/kg, median (range)	5.3 (3.1-11.6)	0.19 (0.04-0.98)
TNC cell dose x 10^7 cells/kg, median (range)	5.8 (2.2-10.9)	4.9 (3.4-16.6)
Clinical Outcomes, 5 years		
Time to neutrophil recovery, median (CI)	19 Days (100%)	25 Days (94%)
Time to platelet recovery, median (CI)	35 Days (93%)	48 Days (74%)
Severe Acute Grade 3-4 GVHD, 100 days	0%	29%
Chronic GVHD	27%	38%
Transplant Related Mortality (TRM)	0%	16%
Disease-free Survival (DFS)	87%	66%
Relapse	13%	18%
Overall Survival (OS)	87%	66%
GVHD/Relapse-free Survival (GRFS)	67%	28%

CONCLUSIONS

These results demonstrate that infusion of NLA101 to augment myeloablative CBT was safe and led to faster neutrophil and platelet recovery. More importantly they showed:

- No severe acute GVHD
- No TRM
- Excellent long-term DFS, OS, and GRFS

In summary, these data suggest that non-HLA matched NLA101 can be infused to enhance the kinetics of hematopoietic recovery and may result in improved clinical outcomes.

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