

Rapid and Robust Immune Reconstitution after Nicotinamide-expanded Cord Blood (NiCord) Transplantation



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Introduction

Nicotinamide-expanded cord blood (NiCord) is a promising alternative source for allogeneic hematopoietic cell transplantation (HCT), a potentially curative treatment for patients with refractory leukemia. Patients with hematologic malignancies and no available matched donor were transplanted with NiCord in a phase I/II study demonstrating median time to neutrophil recovery of 11.5 days (95%CI: 9-14 days) (Horwitz, JCO 2018, in press). However, successful CD4+ immune reconstitution (IR) has been shown to be crucial for infectious and relapse control associated with favorable survival chances (Admiraal JACI 2017). We performed a unique in-depth immune monitoring to evaluate and compare the recovery of immune subsets after NiCord and conventional HCT.

Patients and Methods

Immune monitoring was performed (harmonized sampling, handling and analyses in a central lab) in a random subgroup of 27 (of 36) patients included in the Phase I/II trial. Data were compared with IR in cohorts of adolescent and young adult (AYA) patients at the UMC Utrecht receiving either unmanipulated cord blood transplantation (unCBT) or T-replete unrelated bone marrow transplantation (BMT) for hematological malignancy after myeloablative (MA) conditioning without ATG (Table).

- Primary endpoint: probability of achieving CD4+ IR ($\geq 50 \times 10^6$ CD4+ T-cells / L within 100 days after HCT).
- Secondary endpoints: probability of subset recovery over time of B-cells (immature, transitional, follicular, memory, plasmablasts), CD4+ (Naïve, EM, CM, EMRA) and natural killer (NK)-cells (effector, naïve). We also evaluated CD8 T-cell, dendritic cell (DC), and monocyte counts and subsets (not shown).

Linear-mixed effects modelling in LOESS-regression curves and two-sided log-rank test for univariate comparisons in cumulative incidence plots were applied. LOESS curves were modeled on absolute cell counts during the first year after transplantation. Cell subsets are visualized in pie-charts as percentages of total cells.

Patient Characteristics			
	NiCord	unCBT	BMT
Number of patients (n)	27	27	20
Age at transplant (years; range)	41.5 (13.4-61.7)	15.4 (12.2-22.1)	14.3 (12.1-19.7)
Diagnosis (n)			
Malignancy	27	18	17
Immunodeficiency	0	8	3
Metabolic/inborn error	0	2	0
Myeloablative conditioning (n)	27 (100%)	27 (100%)	20 (100%)
Follow-up (days)	37-365	30-363	40-357

Results

Figure 1: CD4+ IR probability after NiCord HCT

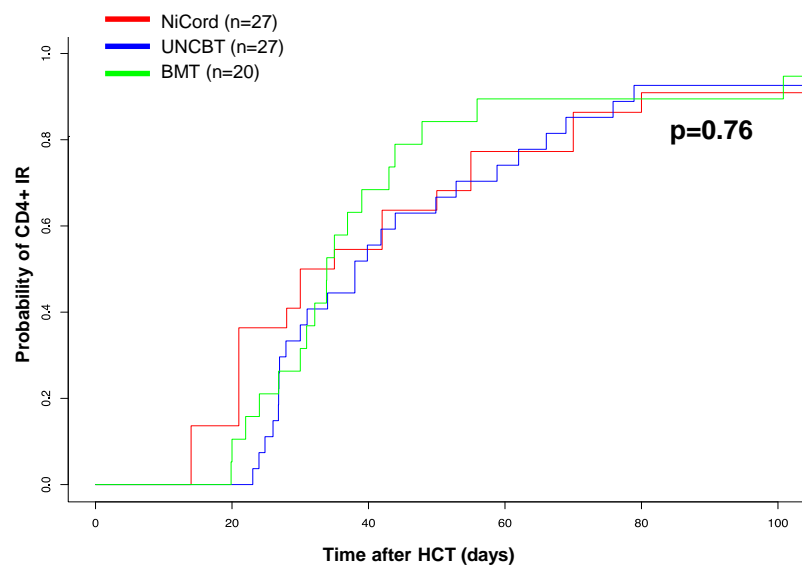


Figure 2: In-depth CD4+ T-cell reconstitution

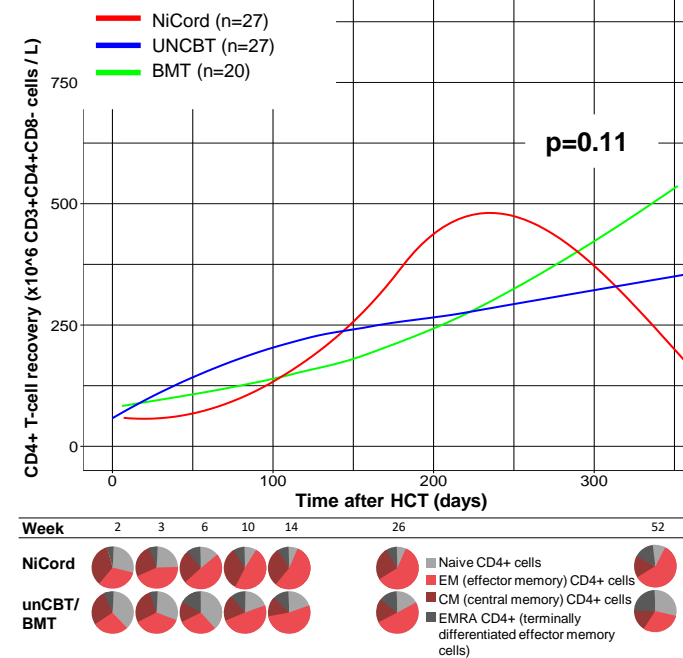


Figure 3: Rapid B-cell reconstitution after NiCord HCT

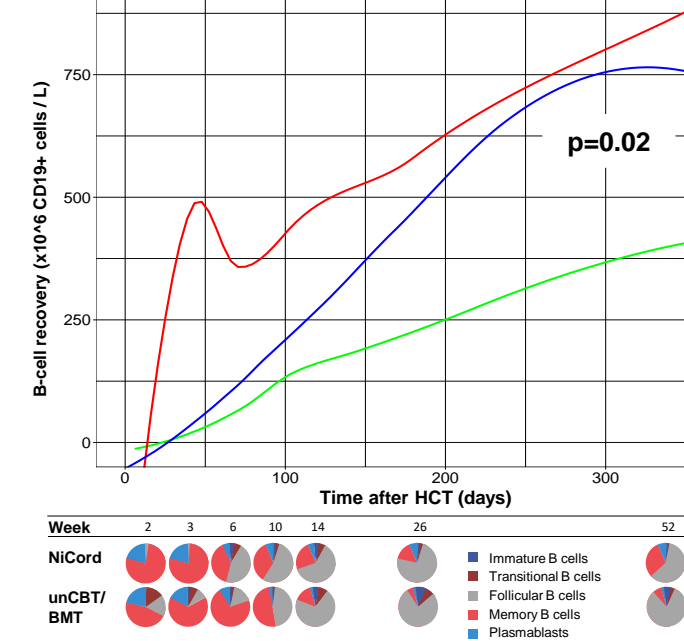
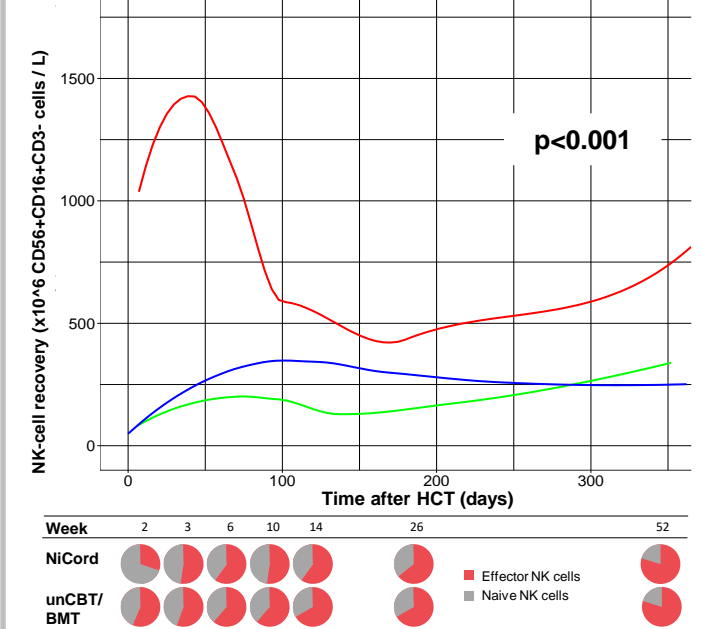


Figure 4: Faster NK-cell reconstitution after NiCord HCT



Summary

- Immune reconstitution of CD4+ T-cell after NiCord was comparable to unmanipulated CBT and BMT
- B-cells and NK-cells recovered more rapidly after NiCord transplantation compared to younger controls receiving unCBT or BMT
- Immune reconstitution after NiCord transplantation was associated with recovery of a broad spectrum of T-, B- and NK-cell subsets comprising a range of effector functions similar to that observed with other graft sources

Conclusions

- Immune reconstitution after transplantation with NiCord was rapid and robust
- Comparison of immune reconstitution in NiCord vs. unCBT will be analyzed in an ongoing Phase III randomized study (NCT02730299)