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Ex Vivo Expanded Cord Blood Natural Killer Cells Combined with Rituximab and High-Dose Chemotherapy and Autologous Stem Cell Transplantation for B Cell Non-Hodgkin Lymphoma

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Relapse is the major cause of failure of high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) for B cell non-Hodgkin lymphomas (B-NHL). Improvement strategies include use in combination with effective immunotherapies. We hypothesized that the combination of rituximab/HDC/ASCT with expanded cord blood (CB)-derived natural killer (NK) cells is safe and active in B-NHL. Patients with B-NHL age 15 to 70 years and appropriate ASCT candidates were eligible for the study. The CB units were selected without considering HLA match with the recipient. The CB NK cells were expanded from day -19 to day -5. Treatment included rituximab on days -13 and -7, BEAM (carmustine/etoposide/cytarabine/melphalan) on days -13 to -7, lenalidomide on days -7 to -2, CB NK infusion (10^8/kg) on day -5, and ASCT (day 0). The primary endpoint was 30-day treatment-related mortality (TRM); secondary endpoints included relapse-free survival (RFS), overall survival (OS), and persistence of CB NK cells. We enrolled 20 patients. CB NK cells were expanded a median of 1552-fold with >98% purity and >96% viability. We saw no adverse events attributable to the CB NK cells and 0% 30-day TRM. At median follow-up of 47 months, the RFS and OS rates were 53% and 74%, respectively. CB NK cells were detectable in blood for 2 weeks, independent of HLA-mismatch status. CD16 expression in donor NK cells was correlated favorably with outcome, and homozygosity for the high-affinity CD16 variant (158 V/V) in CB, but not recipient, NK cells was correlated with better outcomes. Our data indicate that the combination of expanded and highly purified CB-derived NK cells with HDC/ASCT for B-NHL is safe. CD16

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expression in donor NK cells, particularly if homozygous for the high-affinity CD16 variant, was correlated with better outcomes.

INTRODUCTION

Following decades of treating patients with relapsed B cell non-Hodgkin lymphoma (NHL) with high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT), tumor relapse remains the major cause of treatment failure [1]. Although autologous chimeric antigen receptor (CAR) T cell therapy has recently shown improved outcomes compared to HDC/ASCT in refractory or poor-risk relapsed diffuse large B-cell lymphoma (DLBCL) [2,3], >50% of patients still relapse after CAR T cell therapy, most of whom face a dismal prognosis [4,5]. HDC/ASCT could still be useful for these patients if its antitumor efficacy were increased. Promising avenues of improvement include the combination of HDC with effective adoptive immune therapies.

Natural killer (NK) cells are part of the innate immune system and have been implicated in tumor immunity and defense, without the need for prior exposure or sensitization to kill a specific target [6]. Robust NK cell reconstitution has been associated with improved outcomes in NHL patients after HDC/ASCT [7–9]. Unfortunately, autologous NK cells from patients with lymphoma are dysfunctional owing to an unfavorable balance between activating and inhibitory receptors, among other factors [10–12]. Although immunomodulatory drugs, such as lenalidomide [13–16], and cytokines, such as IL-12 [17], may augment NK cell function after ASCT, clinical experience has shown that this is not sufficient to prevent disease progression. Therefore, successful NK immunotherapy activity against lymphoma may require an allogeneic cell source.

The clinical safety of peripheral blood-derived allogeneic NK cell infusions has been demonstrated [18,19]. However, this requires collection of peripheral blood from a normal donor to generate NK cells, which can be logistically cumbersome. To minimize obstacles to collection, our group's interest has focused on NK cells derived from cryopreserved umbilical cord blood (CB), a known source of hematopoietic progenitor cells and an "off-the-shelf" product. We developed a good manufacturing practice (GMP)-grade method of NK cell expansion from thawed CB mononuclear cells based on artificial antigen-presenting cells (APCs) that yields a >1000-fold expansion of NK cells with in vitro and in vivo antitumor activity [20]. Using this technology, we found good tolerability of expanded CB NK cells (up to 10^8 NK cells/kg) combined with high-dose melphalan and ASCT in patients with myeloma [21].

Preclinical data indicate that ex vivo activated and expanded CB NK cells can mediate dose-dependent cytotoxicity against B cell lymphoma lines, which is enhanced in the presence of lenalidomide [22]. Those preclinical results and our clinical experience in myeloma prompted us to study of this novel cellular therapy in patients with B cell lymphoma receiving HDC/ASCT. Concomitant with CB NK cells, patients received rituximab to enhance NK activity through antibody-dependent cellular cytotoxicity (ADCC) and lenalidomide to support NK proliferation and effector function.

METHODS

Patient Population

The study protocol was approved by the Clinical Research Committee and Institutional Review Board of MD Anderson Cancer Center and registered at ClinicalTrials.gov (NCT03019640). Patients provided written informed consent prior to enrollment. Eligibility criteria included age 15 to 70 years; a candidate for ASCT to treat B cell lymphoma, including primary refractory or relapsed DLBCL in response to salvage treatment (excluding primary central nervous system lymphoma), primary refractory or relapsed follicular lymphoma or other indolent B cell histology in response to salvage treatment, and chemosensitive mantle cell lymphoma after first or later line of treatment; and receipt of apheresis of ≥2 million $CD34^+$ cells/kg. Additional eligibility criteria included adequate renal function (creatinine clearance ≥50 mL/minute), hepatic function (serum glutamic oxaloacetic transaminase/ serum glutamic pyruvic transaminase/bilirubin ≤3 times the upper limit of normal), pulmonary function (forced expiratory volume in 1 second/force vital capacity/corrected diffusing capacity of the lungs for carbon monoxide ≥50%), and cardiac function (left ventricular ejection fraction ≥40%); performance status of 0 or 1; no prior whole brain irradiation or any radiation within 1 month of enrollment; no active hepatitis B; and no chronic hepatitis C causing cirrhosis/stage 3 or 4 fibrosis.

There was no requirement for any degree of HLA matching between the CB unit and the patient.

Phenotyping and Tracking of Donor-Derived CB NK Cells

To determine the persistence of donor-derived CB NK cells in the peripheral blood, we used a flow chimerism assay that detected mismatches in HLA genotype between the CB NK cells and the recipient using fluorochrome-conjugated antibodies against HLA antigens. Flow cytometry was performed on a BD LSRFortessa X-20 instrument, and data were analyzed with Kaluza version 2.1 (Beckman Coulter). The phenotype of the circulating NK cells was evaluated using antibodies against CD45 (BD Biosciences; clone HI30) PE-Cy5, CD3 (BD Biosciences; clone UCHT1) APC-Cy7, NKG2C (R&D Systems; clone 134591) AF488, NKp44 (BioLegend; clone P44-8) PerCP; NKG2D (BioLegend; clone 1D11) BV421, NKG2A (BioLegend; clone S19004C) PE-Cy7, NKp30 (BD Biosciences; clone p30-15) BUV395, CD16 (BioLegend; clone 3G8) BV650, NKp46 (BioLegend; clone 9E2) BV711, CD57 (BD Biosciences; clone NK-1) PE-CF594, and Live dead dye (TonBo BioScience) UV450 by multiparametric flow cytometry as described previously [23].

NK cells were identified by gating on a $CD56^{+}CD3^{-}$ cell population from each sample and transformed raw expressions of each marker using hyperbolic arcsine with a cofactor of 150.

We applied cutoffs for expressions at each marker to remove background signal. Each sample was downsized to 5000 cells per sample for analysis. We used Phenograph clustering in Cytotree [24,25] in R to identify subpopulations in the data, with the number of nearest neighbors set at 45. We applied t-SNE to visualize high-dimensional flow cytometry data to 2-dimensional plots. For each cluster, means of transformed marker expression were used to profile expression pattern. Subpopulations with similar marker expression profile were merged into a metacluster when localized close to one another on t-SNE. Data from a patient with unknown status were used only to define metaclusters and their expression profile and excluded from further analysis.

FCGR3A Genotyping

Genomic DNA was extracted from cord blood units using the QIAamp DNA Mini isolation kit (Qiagen) according to the manufacturer's instruction. To identify FCGR3A 158 polymorphisms (SNP ID: rs396991; assay ID: C_25815666_10), predesigned TaqMan MGB probe pairs that detect each allele were purchased from Thermo Fisher Scientific, along with TaqMan Genotyping Master Mix (catalog no. 4371353) [26,27]. Following the manufacturer's instructions, single nucleotide polymorphism genotyping PCR was performed using the AB7500 Fast Real PCR system. 158V/F polymorphism was determined by system software analysis and manual calculation based on the ratio of allele 1 to allele 2.

Treatment Plan

The NK cells used in the treatment of each patient were derived from an individual frozen CB unit. The CB-derived NK cells were expanded in liquid cultures using APC feeder cells at the MD Anderson Cancer Center's GMP Laboratory as described previously [20], starting no less than 14 days (ie, day -19) before their infusion on day -5. Rituximab was administered i.v. at 375 mg/m^2 on day -13. From day -12 to day -7, patients received BEAM (carmustine/etoposide/cytarabine/melphalan). On day -7, patients received a second dose of rituximab at 375 mg/m^2. Lenalidomide was administered orally at 10 mg daily from day -7 to day -2. Steroids were contraindicated from day -8 to day +3.

On day -5, the expanded CB NK cells (10^8/kg) were infused with diphenhydramine and acetaminophen premedication. The NK release criteria included $>$80% $CD16^{+}CD56^{+}$ cells, undetectable APCs ($CD32^{+}CD19^{+}CD56^{+}$) in the viable population, absence of microorganisms on Gram stain, no evidence of contamination by visual inspection, $CD3^{+}$ cell count $<2 \times 10^5$/kg, endotoxin assay $<$5 EU/kg, and total nucleated cell viability $\geq$70%.

Autologous peripheral blood progenitor cells (PBPCs) were infused on day 0. G-CSF was administered s.c. at 5 μg/kg/day from day +5 until neutrophil engraftment. Departmental guidelines for post-transplantation antiemetics, antimicrobials, and blood product transfusions were followed.

Disease assessments with positron emission tomography (PET) or computed tomography scans, and bone marrow exam if indicated, were performed at 1, 3, and 6 months post-HDC and every 6 months thereafter. PET scans were interpreted using the Deauville 5-point scale [28].

To determine the persistence of CB-derived NK cells in the recipient, serial peripheral blood samples were collected on day -4, day 0 (before infusion of PBPC), day + 7, and weekly thereafter until negative results were obtained. As described above, we used a flow chimerism assay based on the mismatch in HLA genotype between the CB NK cells and the recipient.

Statistical Design

The primary outcome for safety monitoring was transplantation-related mortality within 30 days (TRM-30), with a TRM-30 probability of .10 considered unacceptably high. The method of Thall and Sung was used for safety monitoring [29]. Unadjusted RFS and OS were estimated by the Kaplan-Meier method [30].

RESULTS

We enrolled 20 patients between December 2017 and July 2020 (Table 1). This treatment was their first ASCT or adoptive cellular immunotherapy. Their median age was 60 years (range, 33 to 70 years). Seventeen patients had DLBCL, 2 patients had mantle cell lymphoma, and 1 patient had follicular lymphoma (Table 2). One patient with rapidly progressive disease after enrollment was not treated on study. Most of the 19 treated patients had chemosensitive relapsed disease.

The CB NK cells that the patients received were highly mismatched (1/6 match in 18 patients and 2/6 match in 1 patient). CB NK cells expanded a median of 1552-fold (range, 317 to 4767). The infused NK product was highly purified, with a $CD3^{-}CD16^{+}CD56^{+}$ phenotype in a median of 98.91% (range, 97.64% to 99.54%) of the cells and a median total viability of 96.5% (range, 92% to 98%).

Table 1
Treatment Schema

Day	Action
No later than -19	Begin NK cell production
-13	Rituximab 375 mg/m^2 i.v.
-12	Carmustine 300 mg/m^2 i.v.
-11 to -8	Etoposide 200 mg/m^2 i.v. twice daily Cytarabine 200 mg/m^2 i.v. twice daily
-7	Melphalan 140 mg/m^2 Lenalidomide, 10 mg orally Rituximab 375 mg/m^2 i.v.
-6 to -2	Lenalidomide, 10 mg orally
-5	CB NK cell infusion (up to 10^8/kg)
0	Autologous PBPC infusion

There were no adverse events attributable to the CB NK cells, including infusion-related reactions, cytokine release syndrome, neurotoxicity, or graft-versus-host disease. The observed side effect profile of mucositis (8 cases of grade 2), diarrhea (10 cases of grade 2), and uncomplicated neutropenic fever in 14 patients were within the expected toxicity profile of HDC/BEAM. Neutrophil and platelet engraftment occurred promptly in all patients, at median of day 10 (range, 9 to 13) and day 13 (range, 9 to 18), respectively. There were no cases of delayed cytopenia. Post-ASCT

Table 2
Patient Population

Characteristic	Value
Age, yr, median (range)	60 (33-70)
Sex. male/female, n	14/5
Diagnosis, n	
DLBCL Double hit sIPI, median (range)	16 5 3 (0-5)
Mantle cell lymphoma	2
Follicular lymphoma	1
Disease status, n	
Frontline	2 (MCL)
Primary refractory	4
Relapsed	13
Time from initial diagnosis to study enrollment, mo, median (range)	18 (5-111)
Duration of first CR (when applicable), mo, median (range)	6 (0-100)
Prior lines of therapy, n, median (range)	2 (1-4)
PET response at ASCT: CR/PR/PD, n	15 / 3/ 1
HLA matching of CB, n 1/6 match at DR 1/6 match at B 1/6 match at A 2/6 match at B and DR	 9 6 3 1

sIPI indicates secondary International Prognostic Index; MCL, mantle cell lymphoma; CR, complete response; PR, partial response; PD, progressive disease.

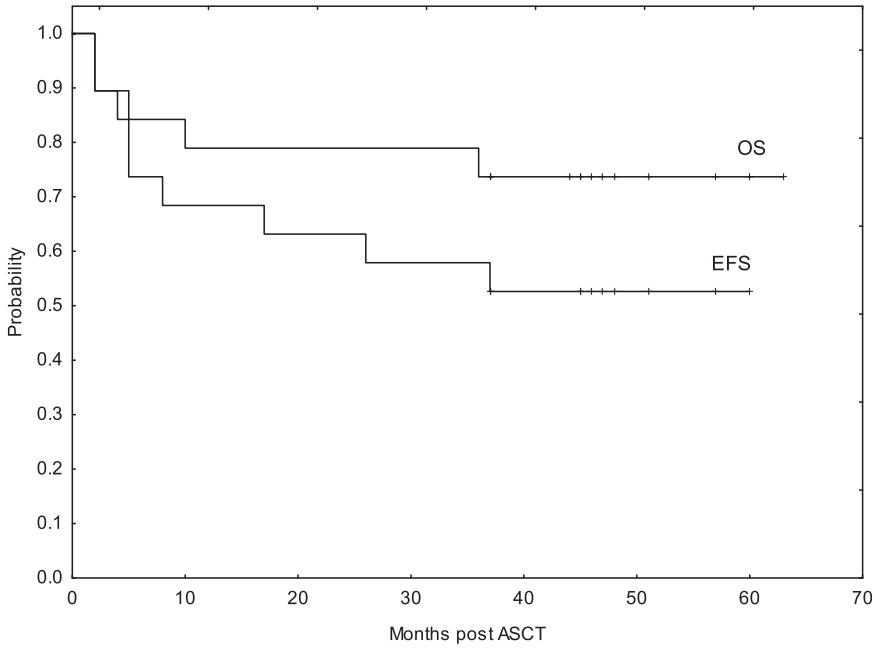

Figure 1. Kaplan-Meier curves of event-free survival (EFS) and OS of the study population.

infections included 1 case each of pneumonia and Coronavirus disease 2019. The 30-day and 1-year TRM were both 0% We saw no cases of secondary myelodysplastic syndrome or acute myeloid leukemia.

At a median follow-up of 47 months (range, 37 to 63 months), 10 patients were alive in remission (event-free survival, 53%) and 14 patients were alive (OS, 74%) (Figure 1).

Multiparameter Flow Cytometry Analysis of NK Cells

We performed flow cytometry analysis of 42 serial samples from 12 patients in 2 subgroups: 19 samples from 6 patients who remained in remission ("remitters") and 23 samples from 6 patients whose lymphoma relapsed at a median of 6 months (range, 2 to 26 months) after ASCT ("nonremitters"). We observed a robust expansion of $CD16^+CD56^+$ CB NK cells in all patients shortly after treatment (Figure 2). Within the first 10 days after infusion, CB NK cells expanded rapidly and composed most of the NK population (87% to 99% in all samples). The number of CB NK cells subsequently declined in both remitters and nonremitters and became nearly absent by the end of the second week. Of note, the persistence of CB NK cells was similar between remitters and nonremitters and was not affected by the degree of HLA mismatch with the recipient.

NK cells from the 2 subgroups had different phenotypes, with remitters exhibiting an increase in activation markers, most notably CD16, in the first month post-ASCT (Figure 3). Remitters and nonremitters showed differing trends in the proportion of total $CD16^+$ NK cells over time. Specifically, remitters experienced a rapid expansion of the $CD16^+$ subset shortly after infusion, with a 6.7-fold increase between days +10 and +20, followed by a subsequent decline. In contrast, the $CD16^+$ cell subset decreased rapidly in the first 3 weeks in nonremitters. The HLA mismatch between the infused CB NK cell product and the recipient allowed us to study the contributions of the donor and the recipient to the $CD16^+$ NK cell pool. Among remitters, the majority of the $CD16^+$ cell population in the first 10 days was CB-derived, accounting for 83.3% of the total $CD16^+$ subset. The proportion of $CD16^+$ cells in recipients increased from 5% to 54% between days +10 and +20 and represented the entire $CD16^+$ NK cells after day +20. In contrast, nonremitters exhibited delayed recovery in both donor and recipient $CD16^+$ NK cells, with reconstitution of recipient $CD16^+$ NK cells observed only after 20 days and constituting approximately only 14% of all cells.

FCGR3A-VV Genotype Is a Predictor of Outcomes

We genotyped the *FCGR3A* gene that encodes CD16 in donor-derived and recipient NK cells from 11 patients. In this small sample we saw that 158 V/V homozygosity (FCGR3A-VV), which results in high-affinity binding of CD16 to Fc-γ in antibodies, correlated with better outcomes when present in the CB NK cells (P = .01) but not in patient NK cells (P = .9) (Figure 4).

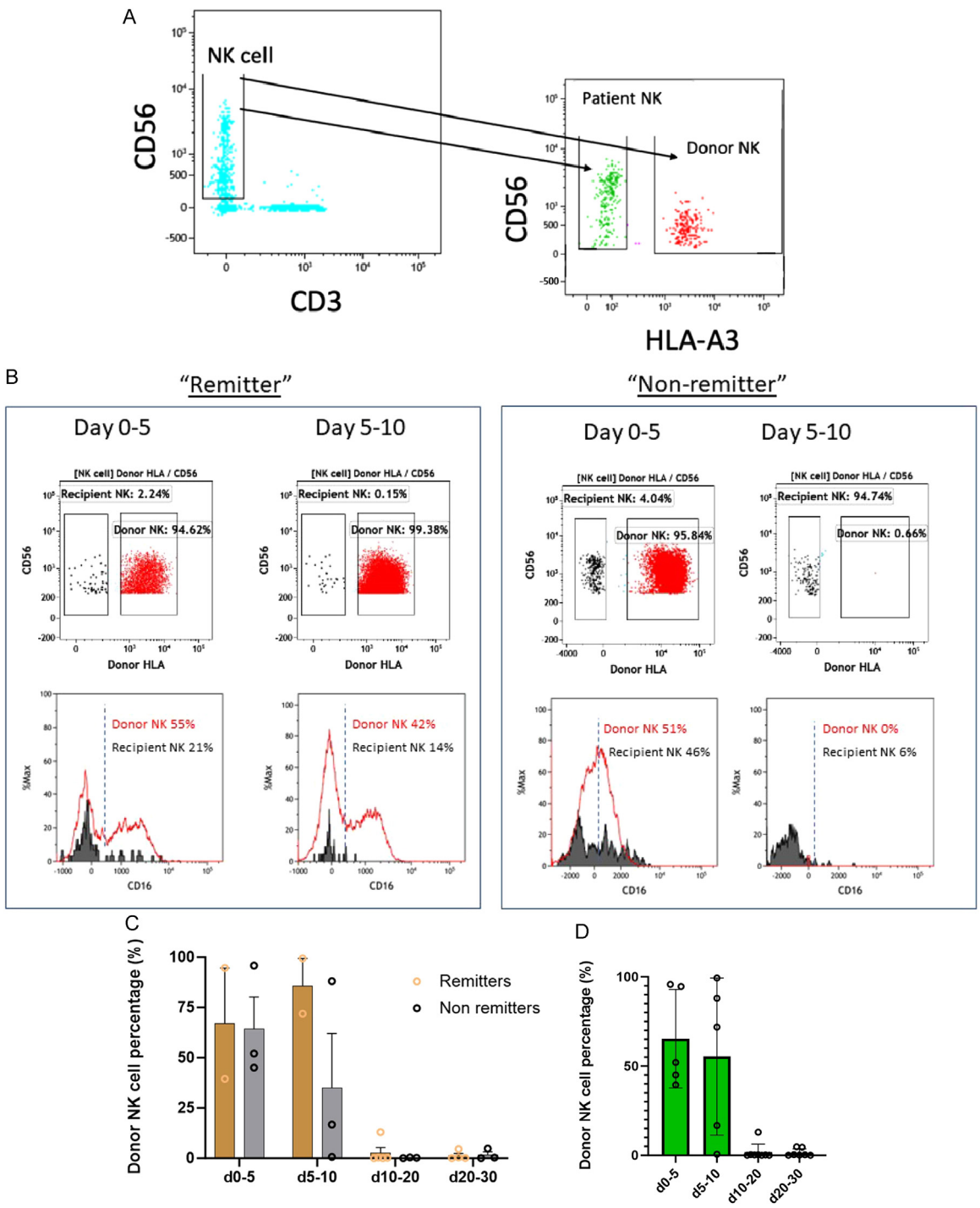

Figure 2. Multiparameter flow cytometry analysis of NK cells. (A) Gating strategy to identify donor and patient NK cells. (B) Expansion of cord blood-derived donor NK cells. The top dot plot shows persistence of donor NK cells by donor-specific HLA staining (red), which is absent on recipient (black) at 2 different time points on both remitters and nonremitters. The bottom panel presents histograms for donor NK cells (red) and recipient NK cells (black) from the top panel, showing the percentages of $CD16^+$ NK cells. (C) Bar graphs of the expansion of cord blood-derived NK cells in remitters (brown bars) and nonremitters (gray bars). (D) Percentage of donor NK cells, combining remitters and nonremitters, at 4 different time points.

DISCUSSION

Our study shows that the combination of expanded CB-derived NK cells with HDC and ASCT is safe in B-NHL patients. Concomitant with CB NK cells, patients received rituximab to enhance NK cell activity through ADCC and lenalidomide to support NK proliferation and effector function. As expected in the absence of cytokine

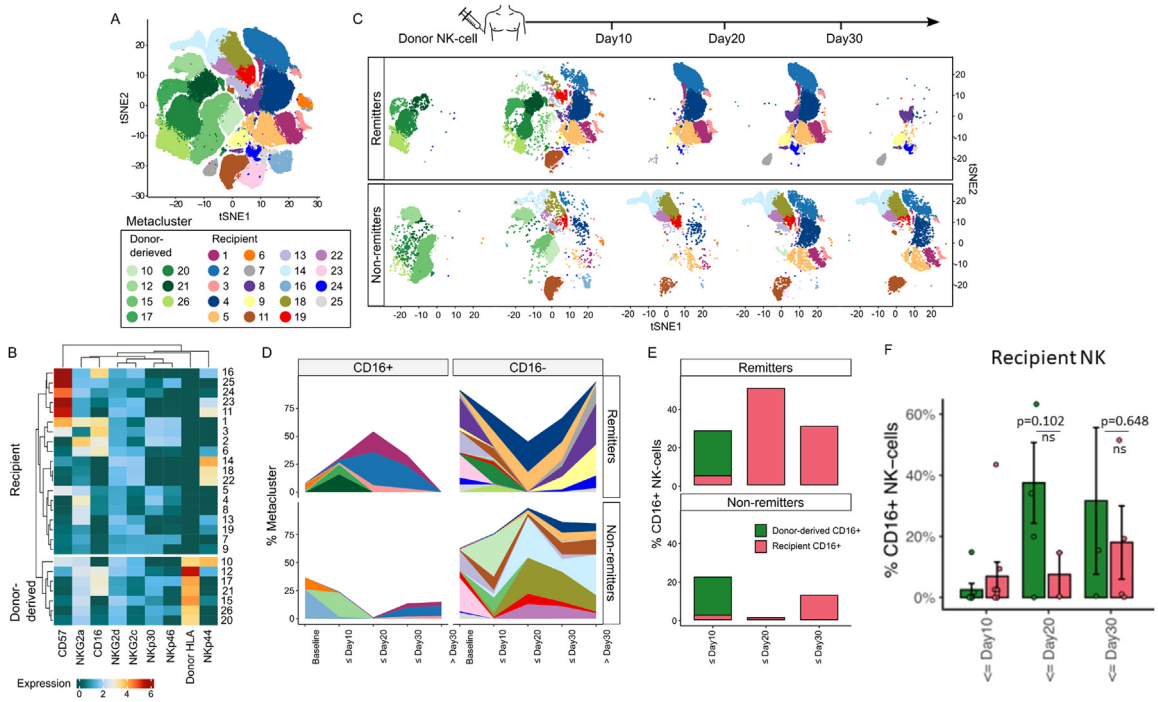

Figure 3. Phenotype analysis of NK cells. (A) Phenograph analysis of all samples overlaid on a t-distributed stochastic neighbor embedding (tSNE) map, identifying 26 distinct NK cell metaclusters. (B) Heatmap summarizing the expression of different markers in each metacluster. (C) tSNE map of samples from remitters (top) and nonremitters (bottom) in each time frame. (D) Analysis of CD16$^+$ NK cells depicting changes in the ratio of each metacluster in samples at each time frame. (E) Distribution of CD16$^+$ NK cells in the first (days 0 to +10) and second (days +10 to +20) time frames after infusion. (F) Expression of CD16 in host NK cells: Percentages of CD16$^+$ recipient NK cells in remitters (green) and nonremitters (pink) at 3 different time points. Each dot represents a patient, and the bar is the mean. Error bars represent SEM. The increase in CD16$^+$ NK cells in remitters was not statistically significant (ns).

support, CB NK cells were detected in the blood for approximately 2 weeks. Importantly for its "off-the-shelf" availability, its the degree of HLA disparity with the patient had no impact on their persistence or on any clinical parameter of toxicity or efficacy.

Expression of CD16, the Fc-γ receptor responsible for binding to IgG complexes and mediating ADCC, on NK cells in the first 2 weeks postinfusion correlated with better outcomes. Furthermore, FCGR3A genotyping in CB NK and patient NK cells showed that the high-affinity V/V variant at amino acid position 158 was predictive of favorable outcomes in CB NK cells but not in patient NK cells—a novel observation in NK cell adoptive immunotherapy. Homozygosity for 158 V/V results in higher CD16 expression and increased binding to monoclonal antibodies, including rituximab [31,32]. Although our novel observations are preliminary owing to our small sample size, they suggest a major role in ADCC by CB NK cells.

In recent years, several groups including ours have further developed allogeneic NK cells for B-NHL by genetic modification to express a CAR targeting a B cell antigen. We previously reported high activity and safety of CB-derived CD19.CAR NK cells given after lymphodepleting chemotherapy in 11 patients with relapsed B-NHL or chronic lymphocytic leukemia [33]. In contrast to nontransduced allogeneic NK cells, NK cells that are genetically modified to express both a CAR and IL-15, a cytokine that plays an important role in NK cell persistence and proliferation, persist for much longer periods. Indeed, in our clinical trial with CB-derived CAR19/IL-15 in B cell malignancies, we could detect the cells for 1 year or longer postinfusion. Similarly [33], Cichocki et al. [34] generated NK cells from induced pluripotent stem cells transduced with CD19.CAR and high-affinity noncleavable CD16, which are currently undergoing clinical testing. Our data also suggest the benefit of banking CD16 158 V/V-specific NK cells for future therapy.

Strengths of our study include the novelty of combining HDC with expanded CB NK cells in a homogeneous fashion and the correlative studies that support our initial mechanistic

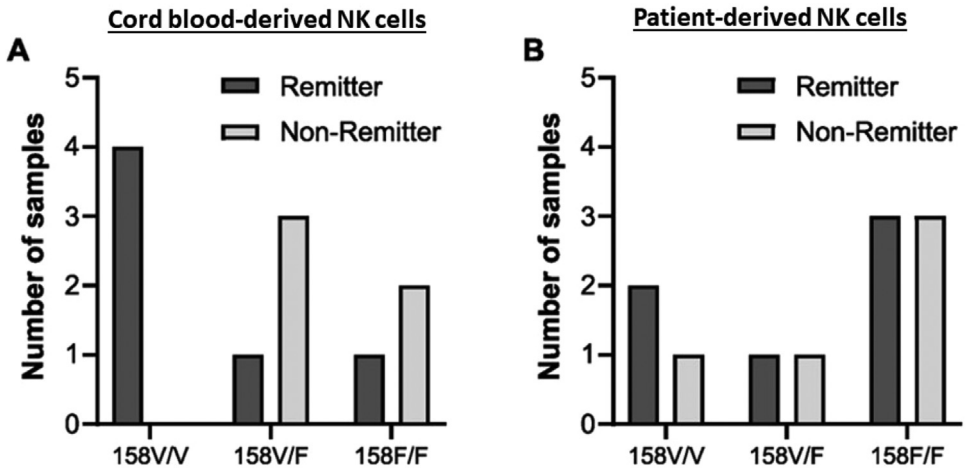

Figure 4. CD16 genotyping of cord blood-derived (A) and patient-derived (B) NK cells.

hypothesis. Weaknesses include the small sample size and the heterogeneity of B-NHL diagnoses, although most patients had high-risk relapsed DLBCL, with a short median first complete response of 6 months. Furthermore, the addition of HDC makes it difficult to establish the relative effect of CB NK cells on patient outcomes.

CONCLUSION

The combination of expanded and highly purified CB NK cells with HDC/ASCT to treat B-NHL is safe. Further development of this strategy by, for example, combining CB-derived CAR NK cells with HDC is warranted.

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Authorship statement: Y.N. designed the research, treated patients, interpreted the data, and wrote the manuscript; P.B. performed and analyzed the correlative studies; I.K. treated patients; K.H.K. performed and analyzed the correlative studies; D.F. performed and analyzed the correlative studies; P.F.T. designed the research and analyzed data; L.G. treated patients; M.B. treated patients; R.B. performed and analyzed the correlative studies; C.H. treated patients; J.R. treated patients; S.S. treated patients; M.D. treated patients; D.M. treated patients; X.Y. performed and analyzed the correlative studies; K.C. performed and analyzed the correlative studies; R.C. treated patients; E.J.S. designed the research, treated patients, and interpreted the data; K.R. designed the research, interpreted the data, and wrote the paper. All authors revised and approved the final version of the manuscript.

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