B05

Phase I Study of Nicotinamide-Expanded Related Donor Natural Killer (NK) Cells for the Treatment of Relapsed/Refractory CD20+ non-Hodgkin Lymphoma

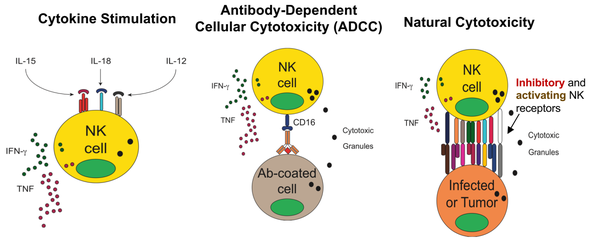
Veronika Bachanova, David H. McKenna, Jr., Xianghua Luo, Todd E. De For, Sarah A. Cooley, Daniel W. Weisdorf, Jeffrey S. Miller.
Blood and Marrow Transplantation and Cellular Therapy Program, University of Minnesota Medical Center, Minneapolis, MN

Masonic Cancer Center, University of Minnesota
Comprehensive Cancer Center designated by the National Cancer Institute

Background

NK Cells

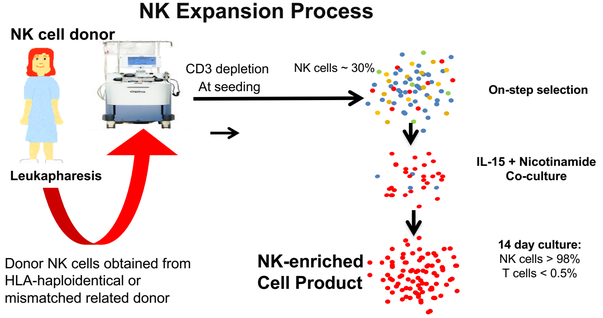
- Natural killer (NK) cells play a critical role in tumor surveillance and cancer cell killing through a variety of mechanisms
- Adoptive transfer of cytolytic NK is an attractive immunotherapeutic approach to the treatment of lymphoma and other malignancies
- However, previous clinical success has been modest due to limited *in vivo* persistence of NK cells and their impaired effector function
- **This phase I study explores the use of haploidentical NK cells that are expanded *ex vivo* with nicotinamide (NAM)**



NAM-NK

- Nicotinamide (NAM) modulates cellular stress, cellular energy, mitochondrial functions and gene expression
- NAM has been successfully used to expand hematopoietic stem cells in umbilical cord blood for allogeneic bone marrow transplantation (1)
- NAM-based technology has been adapted for adult donor NK cells, modulating the characteristics and function of NK cells expanded *ex vivo*
- In preclinical studies, NAM-NK demonstrated cytotoxicity as well as increased homing, proliferation and persistence (2)
- We report preliminary results of a phase I study of NAM-NK in patients with lymphoma and multiple myeloma

NK Expansion Process



Phase I Study Design

Objectives

- Dose escalation phase: Determine maximum tolerated dose of NAM-NK
- Expansion phase: Overall disease response in multiple myeloma and lymphoma

Key Inclusion Criteria for Patients with Lymphoma*

- Age ≥18 to ≤80 years
- Confirmed CD20-positive B-cell non-Hodgkin lymphoma (NHL)
- Evidence of relapsed/refractory disease that has failed conventional therapy
- Relapsed disease at least 60 days after autologous stem cell transplantation
- Relapsed disease at least 4 months after allogeneic stem cell transplantation; no evidence of GvHD
- Measurable disease >1.5 cm in diameter
- Acceptable organ function

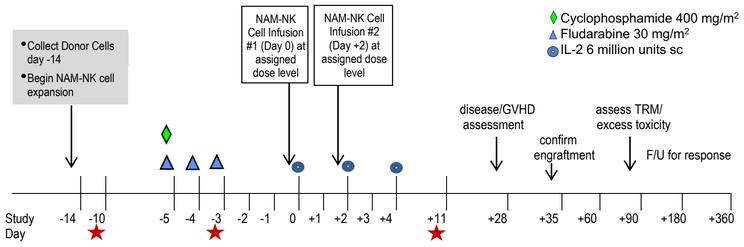
*separate inclusion criteria are delineated for patients with multiple myeloma

NAM-NK Dose Levels

Dose Cohort	TNC dose Dose 1 Day 0	TNC dose Dose 2* Day +2	TNC dose Total Dose
1	1 x 10^7/kg	1 x 10^7/kg	2 x 10^7/kg
2	5 x 10^7/kg	5 x 10^7/kg	10 x 10^7/kg
3	1 x 10^8/kg	1 x 10^8/kg	2 x 10^8/kg

Study Schema

- Donor NK cells are obtained and undergo *ex vivo* expansion
- Patient undergoes lymphodepleting preparative regimen of cyclophosphamide and fludarabine
- Patient receives expanded NAM-NK followed by short course IL-2
- Monoclonal antibodies administered prior to and after NAM-NK infusion



Disease Specific Monoclonal Antibody:

★ E **Elotuzumab** 10 mg/kg *(multiple myeloma patients only)* on Day -10, Day -3, and Day +11
★ R **Rituximab** 375 mg/m² *(B-cell lymphoma patients only)* on Day -10, Day -3, and Day +11

Results

Preliminary Safety Results

- No cytokine release syndrome or neurotoxicity was observed in the first patients treated (n=2)
- Expected short-term neutropenia and thrombocytopenia observed
- No dose limiting toxicity
- No grade 3 or 4 adverse events
- Dose escalation phase is underway

Patient 002: Treatment Course

67 year old patient with follicular lymphoma diagnosed in Oct 2012; Stage IVA; adenopathy in upper and lower abdomen; bone marrow involved

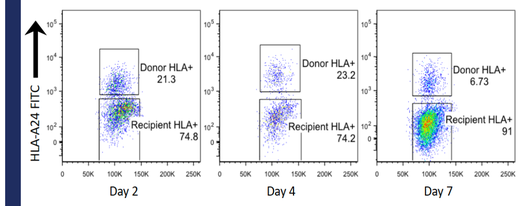
History:

- 12/2012: Front-line therapy: CVP
- 12/2013: Relapse clinically and by CT
- 4/2014: Salvage therapy – Bendamustine Rit x 6 cycles: PR with remaining Left inguinal lymph node (1.9 x 1.3 cm)
- 1/2017: Progression bilateral inguinal LN, left bulky and marrow involved
- 3/2017: R-EPOCH x 2 cycles. Progression
- 7/2017: R-ICE with kinetic failure and progression after 2 cycles

NAM-NK Treatment:
March 2018: Treated at Dose level 1 TNC: 2 x 10^7 cells/kg
CD3: 1.2 x 10^5/kg; NK 1.9 x 10^7/kg

- Treatment tolerated well with expected transient pancytopenia
- **April 2018: Complete clinical and radiologic response**

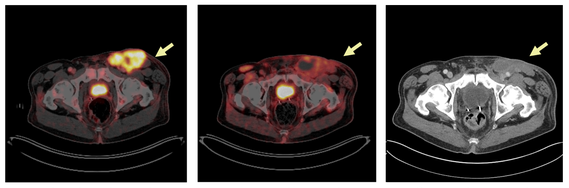
Patient 002: Expansion of NK Cells in Peripheral Blood

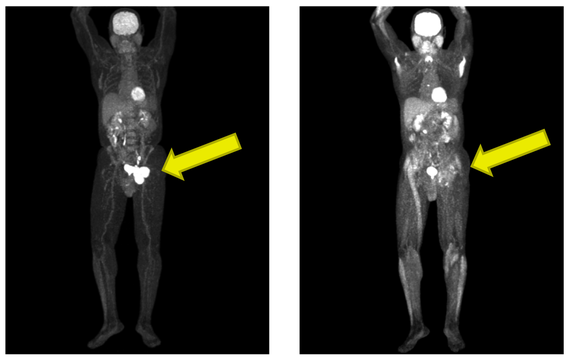


Patient 002: Results

- Symptomatic resolution of bulky inguinal lymphadenopathy
- Complete response by CT/PET scan
- Biopsy of residual mass showed no evidence of lymphoma
- Evidence of expansion of donor NK cells in peripheral blood

Patient 002: Radiographic Complete Response





Conclusions

- Manufacturing of NAM-expanded haploidentical NK cells is feasible and effective
- No infusion reactions were observed
- Preliminary clinical efficacy was observed
- Trial continues to actively enroll eligible patients with non-Hodgkin lymphoma and multiple myeloma

Acknowledgements

ClinicalTrials.gov Identifier: NCT03019666
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References

(1) Horwitz, M, et al JCI12:3121, 2014
(2) Peled, T, Brachya, G, et al: Blood 2017 130:657.