B05

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

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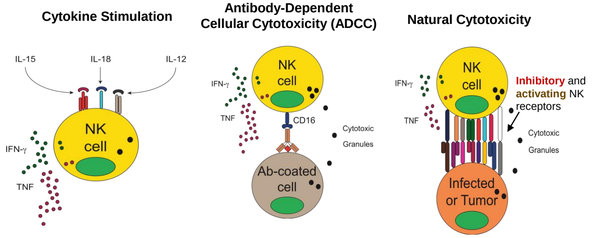
Background

NK Cells

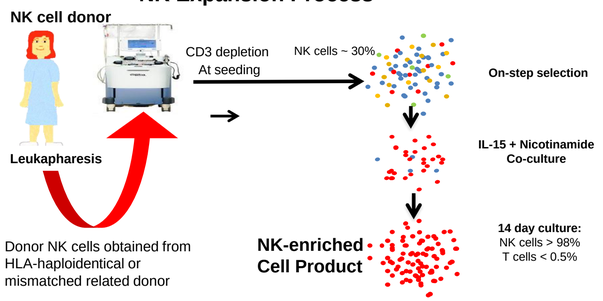
- Natural killer (NK) cells play a critical role in tumor surveillance and cancer cell killing through a variety of mechanisms
- Adoptive transfer of cytolytic NK is an attractive immunotherapeutic approach to the treatment of lymphoma and other malignancies
- However, previous clinical success has been 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

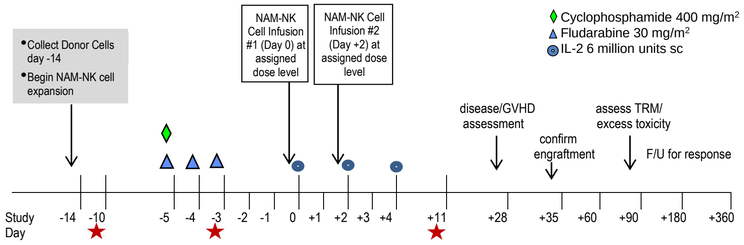
*separate inclusion criteria are delineated for patients with multiple myeloma

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

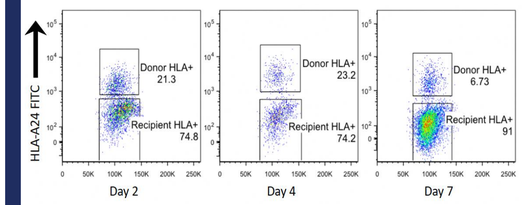
History:

- 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**

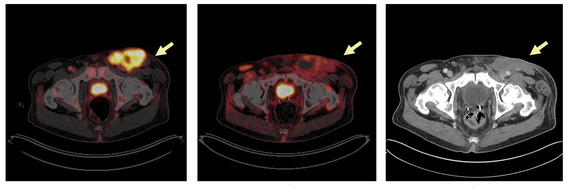
Patient 002: Expansion of NK Cells in Peripheral Blood



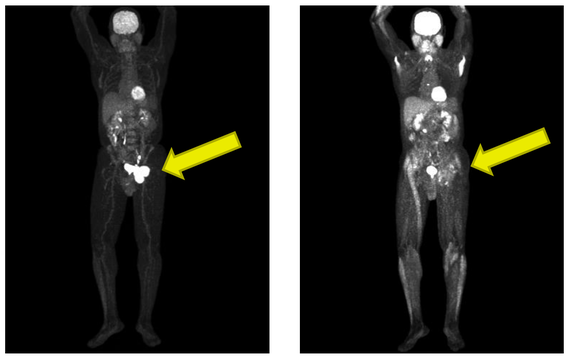
Patient 002: Results

- 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



Pre-treatment | 1-month post | 3-months post



Pre-treatment | Post-NK cell treatment

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.