Poster P004

Expansion, Persistence, and Characteristics of Autologous, BHV-1100 ARMored Memory-Like NK Cells Infused Prior to Autologous Stem Cell Transplant in MRD+, Newly Diagnosed Multiple Myeloma Patients

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CONCLUSIONS

1. BHV-1100 is an antibody-recruiting molecule (ARM) that binds to CD38 target cell antigen and recruits NK cells for ADCC
2. Autologous, BHV-1100 ARMored CIML NK cells have enhanced anti–multiple myeloma activity in vitro and expand and persist in vivo, peaking at 28 days after infusion
3. In a first-in-human study in patients with multiple myeloma undergoing ASCT, no severe or unexpected adverse events were noted with BHV-1100 ARMored CIML NK cells; longer follow-up is required
4. BHV-1100 ARMored CIML NK cells represent an innovative approach to boost autologous cancer immunosurveillance in the context of ASCT for multiple myeloma

INTRODUCTION AND METHODS

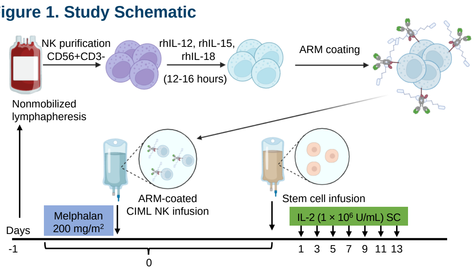
Introduction

- Autologous stem cell transplant (ASCT) improves minimal residual disease (MRD) negativity and prolongs progression-free survival in patients with newly diagnosed multiple myeloma[1,2]
- Multiple myeloma natural killer (NK) cells are dysfunctional, negatively impacting outcomes in patients with multiple myeloma[3,4]
- BHV-1100 is an ARM that binds to CD38 target cell antigen and recruits NK cells for antibody-dependent cellular cytotoxicity (ADCC) without inducing NK cell fratricide
- Allogeneic, cytokine-induced memory-like (CIML) NK cells effectively treat myeloid disorders[5]; however, it is not known whether autologous CIML NK cells can be obtained and, when coated with BHV-1100, if they would improve ASCT outcomes in multiple myeloma
- We designed a first-in-human study of autologous CIML NK cells coated ex vivo with BHV-1100 for MRD+ patients with newly diagnosed multiple myeloma undergoing ASCT

Methods Overview

- In the ongoing phase 1 study (NCT04634435), eligible patients had newly diagnosed MRD+ multiple myeloma and were in first or second remission without prior ASCT or allogeneic stem cell transplant
- The study schematic (**Figure 1**) shows an overview of ASCT with BHV-1100
- The percentage of NK cells (CD56+CD3-) and CD57+, KIR+, and NKG2A+ NK subsets in patients' peripheral blood was assessed using flow cytometry
- Target cell death, CD107a expression, and interferon gamma (IFNγ) production were assessed following a 6-hour co-culture with MOLP8 target cells and the infusion product vs untreated CIML (1:1, 2:1, and 5:1 effector:target ratios), both at the time of infusion and after 24 hours at 4ºC

Figure 1. Study Schematic



Day -1: Patients underwent nonmobilized lymphapheresis. Cells were manufactured in house from lymphapheresis (CD3 depletion, CD56 enrichment using Miltenyi CliniMACS®). NK cells were incubated overnight with IL-12 (10 ng/mL), IL-15 (100 ng/mL), and IL-18 (50 ng/mL) and subsequently coated with BHV-1100.
Day 0: Patients received standard melphalan 200 mg/m^2 myeloablative conditioning, followed by CIML NK cell and then stem cell infusion.
Low dose IL-2 (1 × 10^6 U/m^2) was administered SC (total of 7 doses).
IL, interleukin; rhIL, recombinant human interleukin; SC, subcutaneously.

RESULTS

Patients and Treatment

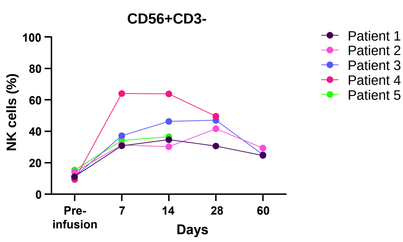
- The in vivo expansion and functional characterization of ARMored CIML NK cells for the first 5 enrolled patients are presented; median follow-up was 191 days
- CIML NK cells were manufactured with a 100% success rate and infused at a target dose of 5-10 × 10^6 cells/kg body weight 24 hours after melphalan 200 mg/m^2 administration
- Patients received 3.9-6.0 × 10^6/kg body weight stem cells
- Engraftment based on recovery of neutrophil count occurred on days 12-14
- Aside from anticipated infusion reactions, no severe or unexpected adverse events were noted
- Longer follow-up is required to assess safety and efficacy

IN VIVO RESULTS

NK Expansion and Persistence

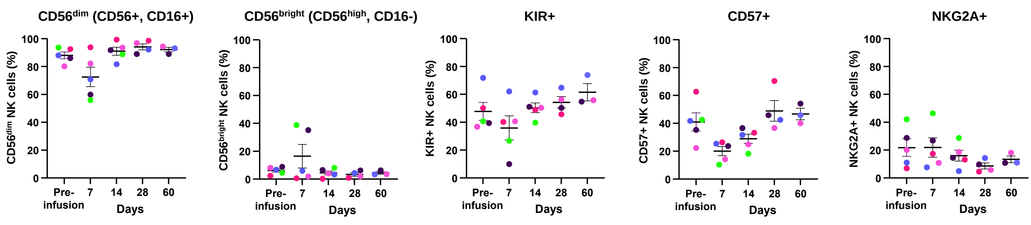
- There was a 3.5-fold expansion of NK cells in the peripheral blood from day 7 (from 11.1% to 41%) to day 28 that persisted until day 60 (25% total peripheral blood mononuclear cells [PBMC]) (**Figure 2**)
- Most expanded NK cells were CD56^{dim}, CD16+, KIR+, and CD57+ (**Figure 3**)
- CD57 and killer cell immunoglobulin-like receptor (KIR) expression increased over time from day 7 to day 60, whereas NKG2A expression decreased, indicating the expansion of mature, activated, and cytotoxic NK cells (**Figure 3**)
- Regulatory T cells increased by day 7 (3% vs 15% total PBMC) and returned to baseline after day 14, most likely reflecting the effect of IL-2 treatment

Figure 2. ARMored NK Cells Expand After Infusion



NK cells (%) is the proportion of total lymphocytes that are CD56+CD3-. Each line represents an individual patient.

Figure 3. ARMored Cells Exhibit an Activated, Mature Cell Surface Signature



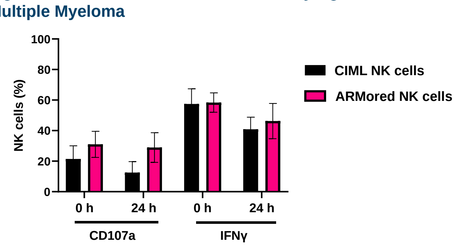
Percentages are the % of total NK cells (CD56+CD3-). Data are presented as mean + standard error of the mean (SEM; n = 5).

IN VITRO RESULTS

Activity Against a Multiple Myeloma Cell Line

- The functional capacity of the infused product was tested in vitro against the MOLP8 multiple myeloma cell line
- Samples of non-infused BHV-1100 ARMored cells were stable for up to 24 hours at 4°C after the time of infusion
- The BHV-1100 ARMored cells had a higher killing capacity compared with untreated CIML NK cells
  - 92.6% vs 91.1% target cell death at 0 hours (2:1 ratio)
  - 90.8% vs 81% target cell death at both 4 hours and 24 hours (2:1 ratio)
- ARMored cells also showed increased CD107a expression (26% vs 14.9%) and IFNγ production (53% vs 37.5%) compared with untreated CIML NK cells at 24 hours (**Figure 4**)

Figure 4. ARMored NK Cells Have Activity Against Multiple Myeloma



NK cells (%) is the proportion of CD56+CD3- total lymphocytes expressing CD107a or producing IFNγ. Data are presented as mean + SEM (n = 4).

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DISCLOSURES

Presenter and coauthor disclosures may be viewed by scanning the QR code.

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