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TCT Meeting 2019 | Nicotinamide-expanded related donor natural killer cells for the treatment of relapsed/refractory multiple myeloma and non-Hodgkin lymphoma: results from the first-in-human phase I study

Emily Smith | Mar 12, 2019

On 20 February 2019, at the 2019 TCT | Transplantation and Cellular Therapy Meetings of ASBMT and CIBMTR in Houston, Texas, USA, Veronika Bachanova, from the University of Minnesota, USA, presented the results of the first-in-human phase I trial (NCT03019666) of nicotinamide-expanded natural killer (NAM-NK) cells for, the treatment of relapsed/refractory multiple myeloma (MM) or non-Hodgkin lymphoma (NHL).[1]

The primary endpoint of this study is to determine the maximum tolerated dose (MTD) of NAM-NK cells whilst maintaining safety, measured by the occurrence of grade 4 or greater adverse events or grade 3 or 4 acute graft-*versus*-host disease. The human leukocyte antigen (HLA)-haploidentical and HLA-mismatched related donor NK cells are expanded with NAM with the aim of enhancing NK cell expansion.[2,3]

Study design:

- Patients had relapsed/refractory MM (RRMM) or CD20-positive NHL
- NAM-NK cell generation:
  - Apheresis was conducted on donors
  - CD3-depleted mononuclear cells were cultured with NAM (5mM) and interleukin-15 (IL-15) (20ng/ml) for 2 weeks
- Patients received:
  - Lymphodepleting chemotherapy
  - Two doses of NAM-NK cells (days 0 and 2) in combination with low-dose IL-2
  - Elotuzumab was given to patients with MM
  - Rituximab was given to patients with NHL
- Nine patients were enrolled and of these, seven were evaluable
- Refractory NHL (n = 5)
  - Follicular lymphoma (FL) (n = 3) and diffuse large cell lymphoma (n = 2)
- RRMM (n = 2)
- Product contained, median, 98% NK cells
- *In vitro* culture with NAM + IL-15 for 14-16 days provided:

- NK cells: 40x increase
- CD62L expression increased from 2.9% to 21%
- CD3 content remained <0.5%

- Three patients received NAM-NK at an initial dose of $2x10^7$/kg (n = 3)
- Four patients then received the 2nd dose level of NAM-NK of $1x10^8$/kg

Safety results:

- At the initial dose:
  - No dose-limiting toxicities (DLTs) were observed
  - Transient neutropenia (n = 3)
  - Neutropenic fever (n = 1)
- At the second dose level:
  - No grade 3/4 adverse events were observed
  - No cytokine release syndrome or neurotoxicity

Response assessment at 2 months:

- Complete metabolic remission (n = 3)
  - FL (n = 2)
  - Transformed lymphoma (n = 1)
- Stable disease (n = 1)
  - MM
- Progressive disease (n = 1)
  - MM

Data shown as host NK cells versus NAM-NK cells

- Analysis by flow cytometry of peripheral blood
- Proliferation of NAM-NK between days 2–7 in all patients (2–55%)
- CD16 expression: 68% *vs* 82%
- Proliferation (median Ki67): 81% vs 99%

These initial first-in-human results have shown NAM-NK cells can be safely administered and persist *in vivo*. They were well-tolerated and demonstrated evidence of clinical activity in both RRMM and CD20-positive NHL, advanced-stage diseases. In the ongoing study, dose escalation will be followed by an expansion cohort at the MTD.

References

1. Bachanova V. et al. First-in-Human Phase I Study of Nicotinamide-Expanded Related Donor Natural Killer Cells for the Treatment of Relapsed/Refractory Non-Hodgkin Lymphoma and Multiple Myeloma. Abstract #242. 2019 TCT Transplantation and Cellular Therapy Meetings of ASBMT and CIBMTR, Houston, Texas, USA

2. Frei G.M. et al. Nicotinamide, a Form of Vitamin B3, Promotes Expansion of Natural Killer Cells That Display Increased In Vivo Survival and Cytotoxic Activity. Blood. 2011. http://www.bloodjournal.org/content/118/21/4035?sso-checked=true

3. Clinicaltrials.gov. Ph I Trial of NAM NK Cells and IL-2 for Adult Pts With MM and NHL. https://clinicaltrials.gov/ct2/show/NCT03019666 [accessed 2019 March 12]