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INTRODUCTION

The innate capacity of natural killer (NK) cells to kill tumor targets has been translated into cancer immunotherapy, with the adoptive transfer of cytokine NK cells an attractive immunotherapeutic approach. However, previous clinical success has been modest due to the limited in vivo persistence of NK cells resulting in impaired effector function. Nicotinamide (NAM) can expand any cell type, including stem cells and NK cells. The innate capacity of natural killer (NK) cells to kill tumor cells is low at <0.5% (<5 × 10⁶ cells) resulting in a 40-fold increase in NK cells and complete response in patients with lymphoma who were previously refractory. We now report 2-year follow-up of patients.

OBJECTIVE

- To evaluate outcomes of GA-201 in combination with rituximab in patients with relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL)

METHODOLOGY

Study Design

- This phase 1 trial (NCT03019666) evaluated the safety and efficacy of GA-201 in patients with R/R multiple myeloma and R/R NHL.
- Following donor apheresis, CD3-depleted mononuclear cells were cultured for 14–16 days with NAM (2.5 mM) and rhIL-2 (1-70 units/mL). In the first 12 days, GA-201 was resulting in a 40-fold increase in NK cells and increased expression of CD107D from 2% to 21%.
- GA-201 contained >98% NK cells, and CD3 content was at <0.5% (+5×10⁶/kg/dose).

Figure 2. Study Design

- Patients received 2 doses rituximab and lymphodepleting chemotherapy, before receiving GA-201 followed by low-dose IL-2 and 3rd dose of rituximab (Figure 2).
- Patients and donors provided written informed consent, and ethics approval was obtained.

Study Population

- Inclusion criteria: >18 years of age with CD20-positive B-cell NHL.
- CD20 expression confirmed by flow cytometry or immunohistochemistry.
- Evidence of R/R disease that has failed conventional chemotherapy.
- Measurable disease >1.5 cm in diameter.
- Human leukocyte antigen (HLA)-haplomatched or mismatched related donor (12-70 years of age).
- Karnofsky Performance Scale score 20%.
- Exclusion criteria:
  - Active, untreated central nervous system (CNS) involvement.
  - Active autoimmune disease requiring immunosuppressive therapy.
  - High donor-specific anti-HLA antibodies titer (mean fluorescence intensity >1000).

Endpoints

- Safety: dose-limiting toxicities
  - Overall response rate, complete response, partial response, duration of response, progression-free survival (PFS), overall survival (OS)
- Biomarker: IL-7 and IL-15 levels

Figure 3. Objective Responses in Patients With NHL Treated With GA-201

RESULTS

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Target NHL</th>
<th>TNC Dose (cells/kg)</th>
<th>GDA-201 cell dose, median in 10⁶/kg (range)</th>
</tr>
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<tbody>
<tr>
<td>DLBCL</td>
<td>4 (3-7)</td>
<td>14.2 (2.4-26.2)</td>
</tr>
<tr>
<td>MM</td>
<td>2 (1-3)</td>
<td>20.2 (2.4-26.8)</td>
</tr>
</tbody>
</table>

Figure 4. OS and PFS in Patients With NHL Treated With GA-201

Currently, for the 2-year follow-up of patients, the following outcomes were observed:

Safety

- The most common grade 3/4 treatment-emergent adverse events were (from) myelosuppression (39%), hypotension (9%), neutropenia (4%), febrile neutropenia (4%), and anemia (4%).
- Adverse events of special interest (cytokine release syndrome, neurotoxic events, graft-versus-host disease, or bone marrow aplasia) were not observed.
- One patient died of Escherichia coli sepsis.

Efficacy

- Nineteen patients were evaluable for response.
  - Overall response rate (ORR) was 74%.
  - Complete response rate (CRR) was 65% (n=13).
  - Among patients with CR, they were 5 with DLBCL and 8 with FL.
  - One patient had partial response (PPR).
  - Four patients undergoing treatment with GA-201 without LD chemotherapy; two patients (FL and transformed DLBCL) had further deepening of response from PR to CR.

Figure 3. Objective Responses in Patients With NHL Treated With GA-201

- At a median follow-up of 11 (range, 3–36) months:
  - 1- and 2-year OS were 50% (95% confidence interval [CI]) 27%–69% and 35% (95 CI) 14%–58%, respectively.
  - 2-year OS was 75% (95 CI) 51%–91%.

CONCLUSIONS

- Cellular therapy using GA-201 with rituximab was well tolerated and demonstrated significant clinical activity in patients with advanced DLBCL and FL.
- Durable complete remissions have been observed in patients with relapsed and refractory NHL.
- A cytokine surge following lymphodepleting chemotherapy appears to be associated with clinical activity.
- Phase 2 studies in aggressive and indolent NHL cohorts are planned using cryopreserved GA-201 product.

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References