LymphomaHub

CLL/SLL, MCL, MZL, FL

CAR-T therapy with or without conditioning chemotherapy: Results from a phase I trial

Sylvia Agathou | May 02, 2019

On 2 April 2019, Mark Geyer and colleagues from the Memorial Sloan Kettering Cancer Center, New York, NY, USA, published in *JCI Insight* the results of a phase I trial. This study investigated the safety and long-term follow-up of chimeric antigen receptor T-cell (CAR-T) therapy with or without conditioning chemotherapy in patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) or indolent B-cell non-Hodgkin lymphoma (B-NHL).

CAR-T therapy has shown great promise for the treatment of patients with R/R CLL or B-cell NHL who cannot be cured with standard of care regimens and who constitute a great unmet medical need. In this single-center, non-blinded, phase I trial (NCT00466531), the investigators sought to evaluate the efficacy and toxicity their CAR-T construct with or without conditioning chemotherapy.

Study design & baseline characteristics

- N = 20 patients included in this analysis:
  - R/R CLL: n = 16 patients
  - R/R B-NHL: n = 4 patients
    - Marginal zone lymphoma (MZL): n = 2
    - Follicular lymphoma (FL): n = 1
    - Mantle cell lymphoma (MCL): n = 1
  - Male patients: 70%
  - Median age (range): 63 (43–75) years
  - Median number of prior lines (range):
    - CLL cohort: 4 (1–11)
    - B-NHL cohort: 8 (6–10)
  - Molecular and cytogenetic abnormalities in the CLL cohort:

Unmutated immunoglobulin heavy-chain variable region gene (IgHV)	n = 9
11q deletion	n = 5

17p deletion or *TP53* loss	n = 4
Complex karyotype	n = 3

- CAR-T construct & infusion:
  - CD28 co-stimulatory domain: 19–28z
  - Median duration of autologous T-cell collection (range) prior CAR-T infusion:
    - CLL cohort: 38 (20–225) days
    - B-NHL cohort: 109 (68–139) days
  - Median $CD4^+$:$CD8^+$ ratio in collected autologous T-cells (range):
    - CLL cohort: 1.9:1 (0.3:1–5:1)
    - B-NHL cohort: 1.9:1 (0.9:1–13.2:1)
  - Median $CD4^+$:$CD8^+$ ratio in infused CAR-T cells (range):
    - CLL cohort: 5.7:1 (0.3:1–0:1)
    - B-NHL cohort: 1.8:1 (0.8:1–3.1:1)
  - Median transduction efficiency (range): 30% (22–59%)
  - Median CAR-T cell product manufacturing (range) for entire cohort: 15 (11–19) days
- Study treatment stages for CLL cohort. The B-NHL cohort followed treatment Stage 3 only:
- Stage 1 (n = 3):
  - CAR-T infusion dose: 1.2–0 x 10^7 cells/kg
  - Conditioning chemotherapy: none
- Stage 2A (n = 1 patient):
  - CAR-T infusion dose: 3.0 x 10^7 cells/kg
  - Conditioning chemotherapy: 1.5 g/m^2 cyclophosphamide (Cy)
  - Outcome: this one patient died 48 hours after CAR-T infusion. This protocol was not used again
- Stage 2B (n = 3):
  - CAR-T infusion dose: 0.40–0 x 10^7 cells/kg (split dose: 1/3 was administered on Day 0 and the rest on Day 1)
  - Conditioning chemotherapy: 1.5 g/m^2 Cy
- Stage 3 (n = 9):
  - CAR-T infusion total dose: 3.0 x 10^7 cells/kg (split dose as above)
  - Conditioning chemotherapy: Investigator's choice:
    - Cy (0.3, 3 or 1.5 g/m^2)

- Fludarabine (Flu; 25 mg/m^2) and Cy (1.5 g/m^2)
- Bendamustine (70 or 90 mg/m^2)

- Five patients in the CLL cohort were allowed to receive continuous ibrutinib treatment up to CAR-T infusion (median: 7 months) and four patients up to leukapheresis (median: 4.8 months)

Key findings

	CLL cohort (n = 16)	**B-NHL cohort (n = 4)**
Median follow-up (range)	40.6 (1.8–79.8) months	-
Median event-free survival	3.1 months	33.4 months
Median overall survival	17.1 months	Not reached
Objective response	38%	-
Complete response (CR) by IWCLL or Lugano criteria, respectively	n = 3/12 (two were MRD negative)	n = 2 (these patients were in CR at the time of CAR-T infusion and remained in CR thereafter)
Stable disease by IWCLL or Lugano criteria, respectively	n = 9	n = 2
Patients remaining in CR at median follow-up of 53 months or 24.7 months, respectively	100% (3/3)	50% (the other patient died 27 months post-infusion due to lymphoma unrelated causes)

- Amongst the patients with CLL, who did not achieve CR (n = 12):
  - Lost to follow-up: n = 1 patient

- Died in active follow-up due to disease progression: n = 8 patients
- Remained alive in active follow-up and received alternative treatment: n = 3 patients
  - Ibrutinib: n = 1
  - Allogeneic stem cell transplantation: n = 1
  - Other investigational therapy: n = 1
- Amongst the patients with B-NHL who did not achieve CR (n = 2):
  - Patients achieving stable disease (SD): n = 2
- *Ex vivo* expansion of T-cells (P = 0.040) and $CD4^+$:$CD8^+$ CAR-T cell ratios were significantly greater in patients receiving ibrutinib on leukapheresis

Safety

Cytokine release syndrome (CRS)

- CRS was observed in all patients
- The second fraction of CAR-T cells was withheld in 6 out of 11 patients with CLL (for whom split-dose infusion had been planned) due to early CRS development (including 4 out of 5 patients who were receiving concomitant ibrutinib)
- CRS severity (total cohort):
  - Grade 1: n = 8 patients
  - Grade 2: n = 10 patients
  - Grade 3: n = 1 patient
  - Grade 5: n = 1 patient died 48 hours after CAR-T infusion (suspected sepsis syndrome)
- Median CRS onset (total cohort): Day 1 post-infusion
- Latest CRS onset (total cohort): Day 3 post-infusion
- Median CRS duration (range): 2 (1–9) days
- Patients receiving tocilizumab for CRS management: n = 3

Neurological toxicity (NT)

- NT was observed in:
  - CLL cohort: n = 6
  - B-NHL cohort: n = 3
- Patients receiving corticosteroids for NT management: n = 2
- Median NT onset (total cohort): Day 2 post-infusion
- Latest NT onset (total cohort): Day 11 post-infusion
- Median NT duration (range): 1 (1–61) days

- NT severity:
  - Grade 3 encephalopathy: n = 2 patients (reversible)
  - Prolonged encephalopathy and dysphasia: n = 1 (gradual improvement to baseline)
  - All other neurological events were considered as Grade 1 or 2 and were reversible:
    - Encephalopathy: n = 5
    - Dysphasia: n = 3
    - Dysarthria: n = 1
    - Hallucinations: n = 1

Other adverse events (AEs)

- Common Grade 3–5 AEs observed in the total cohort:
  - Neutropenia: n = 8
  - Anemia: n = 6
  - Febrile neutropenia: n = 6
  - Thrombocytopenia: n = 5
  - Hypophosphatemia: n = 5
  - Lymphopenia: n = 4
  - Leukopenia: n = 4
  - Hypotension: n = 4
  - Hyperglycemia: n = 4
  - Hyponatremia: n = 4

Conclusions

- All conditioning chemotherapy regimens tested and the 19-28z CAR-T infusions were acceptably tolerated by patients with R/R CLL and indolent B-NHL, with a few patients achieving a durable CR (CLL cohort only)
- Since *ex vivo* T-cell expansion and $CD4^+$:$CD8^+$ CAR-T cell ratios were significantly greater in patients receiving ibrutinib on leukapheresis the authors suggested that ibrutinib may modulate autologous T-cell phenotype

References

1. Geyer M.B. *et al.* Safety and tolerability of conditioning chemotherapy followed by CD19-targeted CAR T cells for relapsed/refractory CLL. *JCI Insight*. 2019 Apr 2;5. pii: 122627. DOI: 10.1172/jci.insight.122627.

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