MultipleMyelomaHub

Patients eligible for transplant

EBMT 2019 | Dual-targeting CAR T-cells with autologous stem cell transplant for high-risk multiple myeloma

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On Wednesday 27 March 2019, during the 45th Meeting of the European Society for Blood and Marrow Transplantation (EBMT) in Frankfurt, Germany, Xiaolan Shi from The First Affiliated Hospital of Soochow University, Suzhou, CH, presented results from the SZ-CART-MM02 study (NCT03455972). The trial investigated the administration of dual-targeting CAR T-cells, in tandem with autologous hematopoietic stem cell transplant (auto-HSCT) in patients with high-risk, newly diagnosed, multiple myeloma (NDMM).[1]

The development of this new treatment regimen was based on the challenge of treating high-risk patients with MM in China where the drugs are expensive, there is no universal healthcare system, there are few novel drugs and only 14% of patients undergo auto-HSCT.[1]

Study design[1]

- Primary endpoints: safety and tolerability
- Secondary endpoints: overall response rate (ORR), duration of response, minimal residual disease (MRD) status, CAR T-cell persistence, progression-free survival (PFS) and overall survival (OS)
- Data cut-off: March 10, 2019
- Median follow-up: 10 (6–17) months

CAR T design[1,2]

- CAR-CD19 second generation T-cells
  - Murine anti-CD19 single chain variable fragment (scFv)
  - Co-stimulator: CD137
  - Lentiviral vector
  - Including an shRNA-IL-6 silencing property aimed to increase safety
- CAR-BCMA third generation T-cells
  - Humanized anti-BCMA scFv
  - Co-stimulators: CD28 and CD134
  - Lentiviral vector
  - The humanized BCMA scFV combined with two co-stimulators aimed to improve efficacy and persistence

Patient characteristics and definitions[1,2]

- Patients with high-risk NDMM aged 18–65 (N = 10)
  - High risk was defined as the presence of:
    - Genetic abnormalities (del(17p), t(4;14), t(14;16),t(14;20), p53 mutation, 1q gain)
    - R-ISS stage III
    - Type IgD or IgE
    - Extramedullary infiltration
    - ≤ Partial response (PR) after 4 cycles of bortezomib, doxorubicin and dexamethasone (PAD) triplet induction
  - One patient had IgD
  - Four patients had high-risk cytogenetics including one with complex abnormalities
  - Four patients had R-ISS stage III disease
  - Six patients had ≤PR to induction

Treatment regimen[1,2]

- T-cell apheresis
- Induction: 4 cycles of PAD
- Auto-HSCT
  - Conditioning: bulsulfan and cyclophosphamide
- CAR T-cell infusion:
  - CAR-CD19 T-cells: 1 x 10^7/kg on day 0
  - CAR-BCMA T-cells: 5 (2–6) x 10^7/kg
    - Split dose: 40% on day 1 and 60% on day 2
  - Given between day 14–20 after auto-HSCT
- Maintenance after CAR T: immunomodulatory drugs only

Efficacy[1]

- BCMA expression of >30%: 100% (10/10)
- CD19 expression: 30% (3/10)
- ORR: 100% (10/10)
- All patients were monitored for ≥6 months

Table 1: Best responses to treatment regimen over time (n = 10)

	After induction	After auto-HSCT	Day 7	Month 3	Latest
Complete response (CR)	30%	40%	40%	20%	10%
Stringent CR	0%	0%	0%	20%	70%
Very good PR	10%	20%	40%	60%	20%
PR	40%	40%	20%	0%	0%
Stable disease	20%	0%	0%	0%	0%

- MRD negativity in bone marrow by 10-colour multi-flow cytometry
  - After auto-HSCT: 44.4% (4/9) ($<10^{-4}$)
  - After CAR T (latest): 60.0% (6/10) ($<10^{-6}$)

Safety: acute toxicities[1]

Cytokine release syndrome (CRS) occurred in 100% of patients (10/10). Of these, 5 were grade 1 events and 5 were grade 2 events. Table 2 below summarizes the hematological toxicities.

Table 2: Acute hematological toxicities, occurring ≤2 weeks post-infusion (n = 10)

	Grade 1	Grade 2	Grade 3	Grade 4	Total
Decreased white blood cell (WBC) count	40%	10%	10%	0%	60%
Decreased neutrophil (Neu) count	20%	50%	10%	0%	80%
Anemia	10%	60%	30%	0%	100%
Decreased platelet count	20%	20%	40%	20%	100%

Non-hematological toxicities included, fever (100%), fatigue (100%), prolonged activated partial thromoplastin time (70%), elevated troponin T (40%), hypotension (20%), increased transaminase (10%) and atrial flutter (10%). No grade 4 events of non-hematological toxicities were reported, and only the two incidences of hypotension were considered grade 3 events.

Other considerations regarding acute toxicities included:

- Total: 9 hospital stays (9–14 days)
- No tocilizumab or corticosteroids were administered
- Low-dose vascular active drugs were used in two patients
- No patients were transferred to intensive care units
- No treatment-related mortality was reported
- There were no serious CRS or neurologic complications

Safety: chronic toxicities[1]

No grade 4 events of chronic toxicity were reported. The most common chronic hematological toxicities mirrored those reported as acute events during the trial whilst the most common chronic non-hematological toxicities occurring in ≥20% of patients were; hypogammaglobulinemia (90%), infection (40%) and edema (20%).

CAR T expansion[1]

It was shown that the CAR T-cells were amplified and could be detected for more than 1 year after infusion. In patients with high-risk disease, the peaks of CAR T-cells appeared later, but were sustained for longer, when compared to patients with relapsed/refractory disease.

Conclusion

Tandem auto-HSCT with anti-CD19 and anti-BCMA CAR T-cell infusion may provide an alternative consolidation treatment for patients with high-risk MM. Toxicities reported thus far appear mild and have been clinically manageable with all patients reporting ongoing responses.

The authors hypothesize that the immune system may be remodeled following auto-HSCT, which may contribute to a higher expansion of CAR T-cells.

References

1. Shi X. *et al.* Tandem auto-SCT and combined infusion of CD19 and BCMA-specific CART cells for high risk MM. Abstract OS12-1 and oral presentation. 2019 March 27. 45th Annual Meeting of the European Society of Blood and Marrow Transplantation (EBMT), Frankfurt, DE
2. Shi X. *et al.* Tandom Autologous Transplantation and Combined Infusion of CD19 and Bcma-Specific Chimeric Antigen Receptor T Cells for High Risk MM: Initial Safety and Efficacy Report from a Clinical Pilot Study. Blood. 2018 Nov 21. DOI: 10.1182/blood-2018-99-117964