CD19-Directed CAR T-Cell Therapy in Waldenström Macroglobulinemia: Initial Experience in Two Clinical Trials

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Abstract

- Waldenström macroglobulinemia (WM) is a treatable, but incurable, disease, and relapsed/refractory (R/R) disease can cause significant morbidity and mortality.
- Chimeric antigen receptor (CAR) T cell therapies have demonstrated efficacy in B cell non-Hodgkin lymphomas, but had not been evaluated in WM.
- 3 patients with R/R WM were included in 2 clinical trials evaluating anti-CD19 CAR-T therapy.
- No patients had grade ≥3 adverse events, including CRS and neurotoxicity.
- All 3 patients had at least a clinical response to CAR T, including 1 MRD-negative complete remission (CR).
- All 3 patients eventually had disease progression 4-26 months after treatment.

Background

Waldenström macroglobulinemia (WM) is a lymphoma characterized by neoplastic proliferation of lymphoplasmacytic lymphoma (LPL) cells that infiltrate the bone marrow and other organs and secrete monoclonal IgM paraprotein.[1] Bruton tyrosine kinase (BTK) inhibitors, proteasome inhibitors, chemotherapy, and anti-CD20 monoclonal antibodies are effective, but a subset of patients develop treatment-refractory WM and die of their disease.[2,3]

Anti-CD19 directed chimeric antigen receptor (CAR) T-cell therapy is now an established treatment modality in several B cell leukemias and lymphomas.[4] Given these encouraging results and usually strong CD19 positivity of WM clones, CAR T cell therapy is an intuitive option in patients with WM who have exhausted other treatment options.

Materials & Methods

Patients with relapsed/refractory (R/R) WM were included in two phase I clinical trials evaluating the safety and activity of autologous CD19-directed CAR T therapy for lymphoid malignancies. Trial NCT00466531 evaluated a 19-28ζ CAR T product similar to that seen in axicabtagene ciloleucel. Trial NCT03085173 evaluated CD19-targeted 19-28ζ 'armored' CAR T cells engineered to co-express 4-1BBL, another co-stimulatory signal. All patients received bridging therapy after apheresis, followed by fludarabine/cyclophosphamide lymphodepletion prior to CAR T infusion.

Patients and Treatment

Patient Characteristics

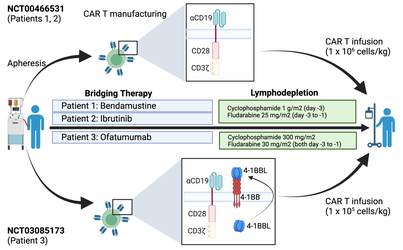
Patients 1 and 2 were treated on protocol NCT00466531, and Patient 3 on NCT03085173. All were female and were 65-74 years of age. All had received at least 5 prior lines of therapy, including anti-CD20 containing chemoimmunotherapy, ibrutinib, and bortezomib. At time of CAR T therapy, patients 1 and 2 had cytopenias requiring transfusion support, and patient 3 had hyperviscosity requiring plasma exchange.

Baseline Characteristics	Patient 1	Patient 2	Patient 3
Age, gender	73, female	75, female	64, female
Genotype	MYD88 p.L265P CXCR4 p.S342fs TP53 p.R175H/R196Q	MYD88 p.L265P Loss of MYB and ATM by FISH	MYD88 p.L265P DNMT3A p.R823K
Time from diagnosis to CAR T	12.1 years	10.4 years	10.2 years
Prior lines of therapy (best response by IWWM criteria)	Rituximab (PR) R-Fludarabine (PR) R-Bendamustine (VGPR) Duvelisib (NE) Ibrutinib (PD) BDR -> R-Bortezomib maint (MR) IMO-8400 (TLR antagonist) (NE) Ofatumumab + Bendamustine (MR)	Rituximab (PR) R-Bendamustine (PR) BDR (PR) Venetoclax (MR) Ibrutinib (PR) Ibrutinib/Ofatumumab (PD)	Rituximab + Bortezomib (PR) Rituximab + Bendamustine (PR) Ibrutinib (PD) Ofatumumab + Cyclophosphamide + Fludarabine (CR, MRD+ on BM) Ofatumumab (PD)
Treatment indication	Transfusion-dependent anemia, thrombocytopenia	Transfusion-dependent anemia	Hyperviscosity
Pre-treatment IgM	2,570 mg/dL	3,789 mg/dL	7,520 mg/dL

Treatment

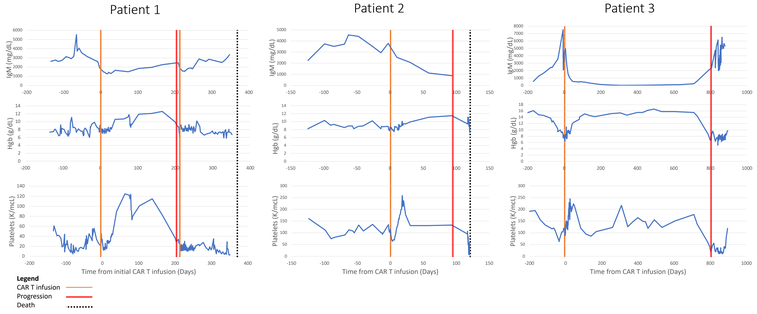
After T cell apheresis, patients received bridging therapy with bendamustine (Patient 1), ibrutinib (Patient 2), or ofatumumab (Patient 3). All received lymphodepleting therapy with cyclophosphamide and fludarabine. Patients 1 and 2 received a second-generation anti-CD19 CAR T cells with a CD28ζ costimulatory domain. Patient 3 was treated with "armored" 19-28ζ/4-1BBL CAR T cells, expressing CD28ζ and 4-1BB ligand (4-1BBL), which activates endogenous 4-1BB as an additional costimulatory signal.

Patient 1 was re-treated with a second dose of the same CAR T cell product after developing clinical progression of disease, 7 months after first CAR T infusion. Patient 2 resumed ibrutinib, which they had been taking as bridging therapy, on day 20 after CAR T infusion, as permitted per protocol.



Efficacy

Patient 3 had a complete response with negative minimal residual disease by flow and molecular analysis, with relapse 26.5 months after CAR T therapy. Patient 2 had a partial response lasting 4 months followed by progression requiring further therapy. Patient 1 had stable disease by IWWM criteria, but had significant improvement in transfusion-dependent cytopenias and was transfusion-independent for 6 months after treatment, with progression 6.8 months after CAR T infusion. Patient 1 received a 2nd CAR T infusion 7 months after the first infusion, with progression of disease as best response.



Response	Patient 1	Patient 2	Patient 3
Best Response	Stable disease by IgM Hematologic response	PR	CR, MRD-negative
Vital Status	Deceased	Deceased	Alive
Cause of Death	Disease	Sepsis 2/2 PsA bacteremia	N/A
PFS (months)	6.8	4.0	26.5
OS (months)	12.4	4.0	Not reached

Safety

All 3 patients had grade 1-2 cytokine release syndrome (CRS), with no grade ≥3 CRS; no patients required tocilizumab. One patient had grade 2 neurotoxicity which resolved in 24 hours with steroids; no other neurotoxicity, and no grade ≥3 treatment-related adverse events were observed.

Two patients died after receipt of CAR T, both after clinical progression of disease. Patient 2 was treated with ofatumumab and ibrutinib after progression, and died of influenza A and pseudomonas infection. Patient 1 died of progression of disease 12.4 months after treatment.

Toxicity	Patient 1	Patient 2	Patient 3
CRS	Grade 1	Grade 2	Grade 2
Neurotoxicity	None	None	Grade 2
Infections	None	None	None
Other	Grade 1 peripheral edema Grade 2 nasal congestion Grade 2 anemia Grade 1 rash	Grade 1 edema Grade 1 alopecia Grade 1 pleural effusion Grade 2 hypothyroidism	Grade 2 dyspnea Grade 2 elevated bicarbonate Grade 2 anemia Grade 1 diarrhea Grade 1 nausea

Treatment Resistance – Tumor Biology

Bone marrow B cell and plasma cell content, along with CD19 expression, were assessed before CAR T therapy, within 1–4 weeks after CAR T administration, and at time of disease progression. In all patients CD19 expression by malignant B cells was appreciated prior to therapy. CD19 expression on malignant B cells was also present in all three patients at time of disease progression. In Patient 1, there was a decrease in B cell CD19 expression by mean fluorescence intensity (MFI) at time of progression after CAR T therapy, which may suggest that antigen escape contributed to resistance.

	Pre CAR T		Residual Disease Post-CAR T		At progression	
Patient 1						
B cell: Plasma cell ratio	3:2		2:3		10:1	
CD19 expression (MFI)	B: 2635	PC: 390	N/A	N/A	B: 1120	PC: 786
Patient 2						
B cell: Plasma cell ratio	22:1		45:1		>30:1	
CD19 expression (MFI)	B: 18554	PC: N/A	B: 20897	PC: N/A	B: 20504	PC: N/A
Patient 3						
B cell: Plasma cell ratio	6:1		1:20		7:1	
CD19 expression (MFI)	B: 2652	PC: 1866	No B cells	PC: 58.6	B: 5304	PC: 4606

Key Findings

- This is the first reported series of patients treated with CAR T therapy for R/R WM.[5]
- CAR T cells were relatively safe in WM, with similar toxicities to those seen with CAR T in other diseases. No grade ≥3 treatment-related events were observed.
- CAR T therapy has activity in R/R WM, with all patients attaining a meaningful response.
- Responses to CAR T therapy were of variable duration, from 4-26 months duration.
- While preclinical models suggest antigen escape via CD19 loss and plasmacytic differentiation may lead to CAR T resistance, CD19 loss was not reliably identified in this cohort.
- Further investigation of CAR T for R/R WM, and mechanisms of WM resistance, are warranted.

References

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