Anti-CD19 CAR T cells: the Balance of Efficacy and Toxicity

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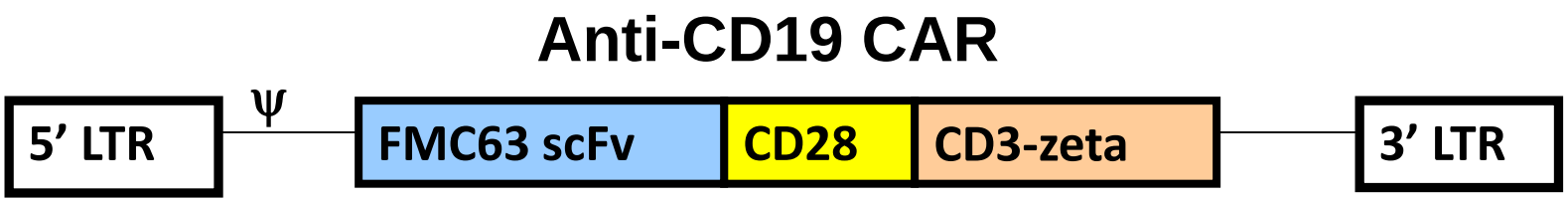
T cells can be genetically engineered to express an anti-CD19 chimeric antigen receptor

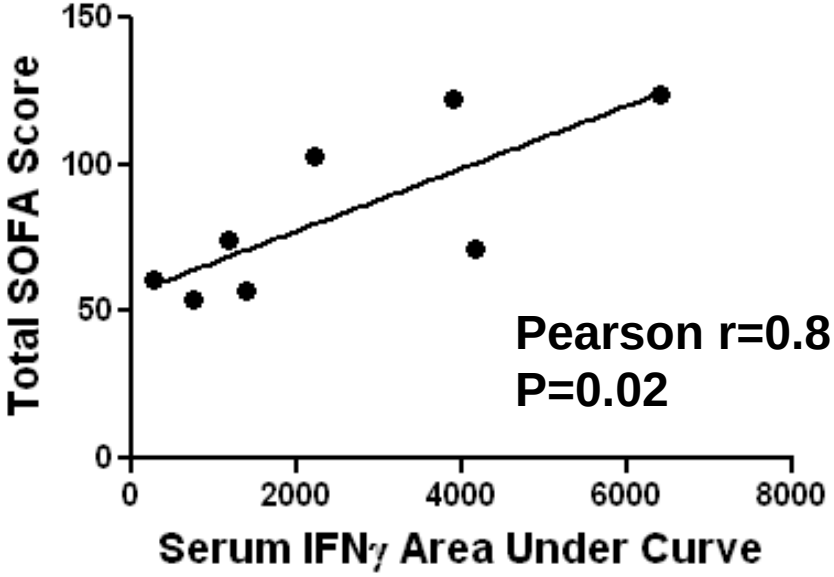
- The anti-CD19 CAR contains a CD28 moiety and is encoded by a gammaretroviral vector.
- In vitro CAR-transduced cells make a variety of cytokines in a CD19-specific manner.
- T cells were stimulated with the anti-CD3 monoclonal antibody OKT3 before transduction.
- Preparation took 10 days for each patient.

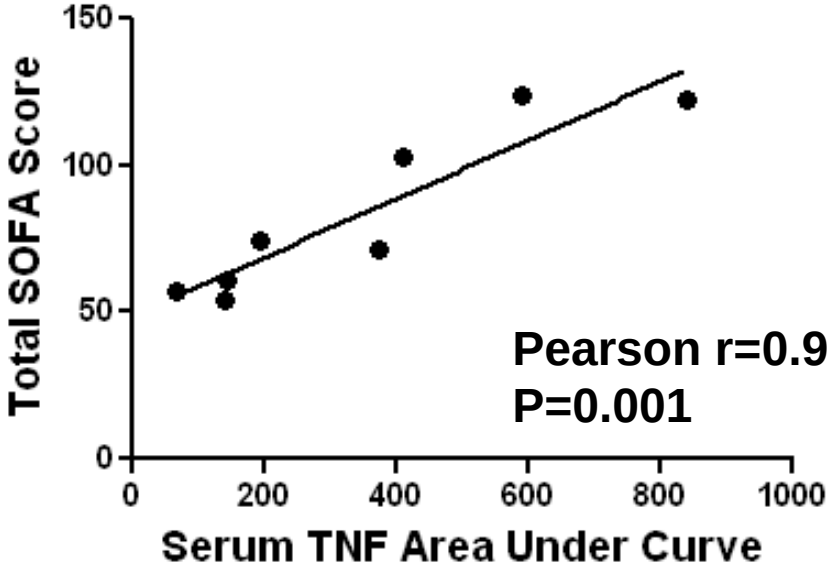


Kochenderfer et al. Journal of Immunotherapy 2009

Acute toxicity after CAR-transduced T cell infusion correlated with the serum levels of IFNγ and TNF

- Patients experienced transient hypotension, fever, and obtundation
- SOFA stands for sequential organ failure assessment
- The SOFA score is a method of quantifying cardiovascular, renal, hepatic, CNS, and bone marrow dysfunction



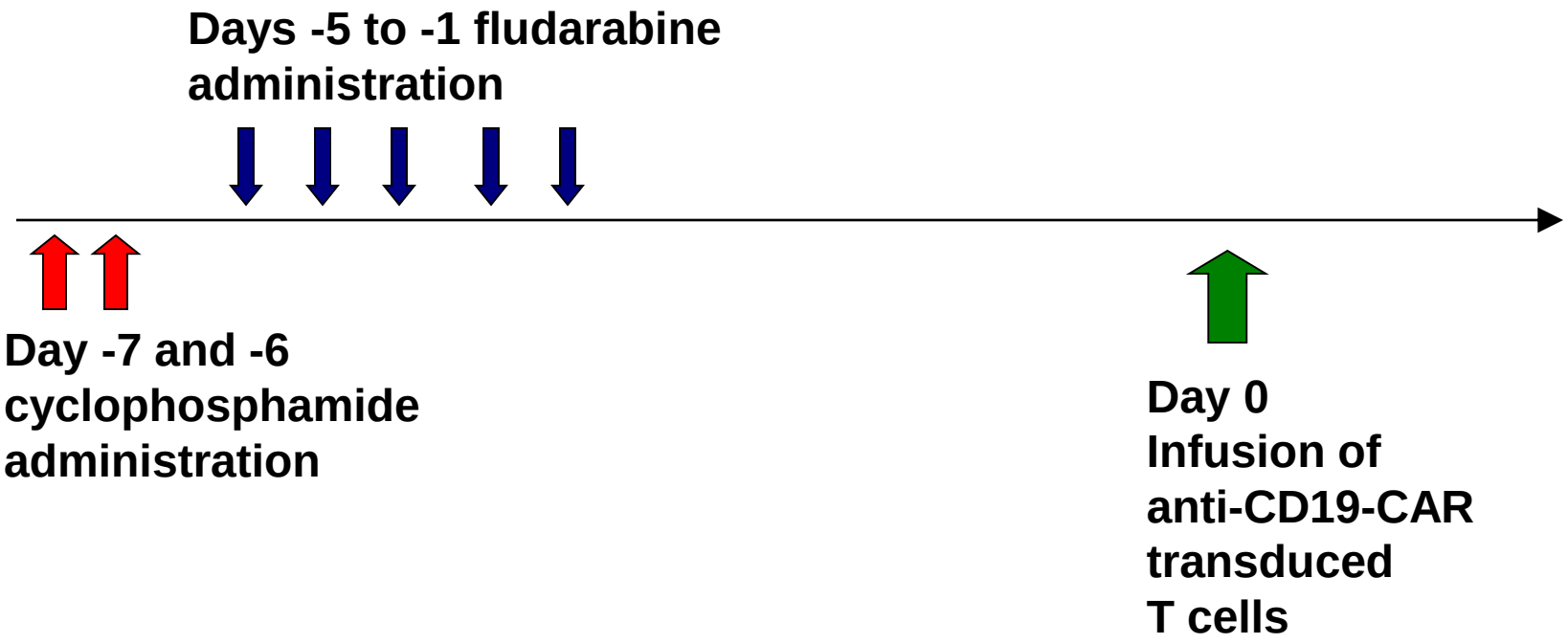


Kochenderfer et al. Blood 2012

Eligibility criteria

- **ECOG 0 or 1 performance status**
- **Normal cardiac ejection fraction (greater than 55%)**
- **Normal renal function**
- **Platelet count at least 50,000/microliter**
- **No central nervous system malignancy (normal pretreatment brain MRI is required)**

Treatment plan 1: anti-CD19 CAR protocol with high-dose chemotherapy



Cyclophosphamide: 60 or 120 mg/kg total dose

Fludarabine: 25 mg/m^2 daily for 5 dose

Cells dose 5x10^6 to 1x10^6 CAR+ T cells/kg

Summary of anti-malignancy responses in high-dose chemotherapy patients

- 15 patients treated
- 9 with DLBCL, 6 with indolent B-cell malignancies
- 12 of 15 patients had chemo-refractory lymphoma or lymphoma that relapsed after autologous stem cell transplantation
- 10 patients obtained CRs, 2 patients obtained PRs, 1 patient had stable lymphoma, and 2 patients were not evaluable

Grade 3 or greater toxicities in patients treated with high-dose chemotherapy

Patient	Grade 3 or greater toxicities
1	Hypotension, confusion, acute renal failure, fever
2	Fever, confusion/aphasia, facial nerve palsy, headache, urinary tract infection
3	Headache, fever, confusion, hypotension
4	Nausea, hypoxia, dyspnea, tachycardia, fever, bacteremia, malaise, vascular leak syndrome, death
5	None
6	None
7	Influenza, fever, headache, bacteremia
8	Fever, pneumonitis, hypotension, hypoxia, bacteremia, obtundation, elevated creatinine
9	Fever, aphasia, myoclonus
10	Bacteremia, fever, fatigue
11	Bacteremia, urinary tract infection, fever
12	Fever, urinary tract infection, bacteremia, upper extremity thrombosis
13	Dyspnea, upper extremity thrombosis, urinary tract infection, creatinine increase, hypotension
14	Hypotension, fever
15	Fever, aphasia, encephalopathy, neuropathy, gait disturbance

Note: all patients had cytopenias due to chemotherapy

Summary of toxicities

- One patient with primary mediastinal B-cell lymphoma and pre-existing heart dysfunction died suddenly 16 days after infusion of CAR T cells. No cause of death was established at autopsy. Cardiac arrhythmia was the most likely etiology.

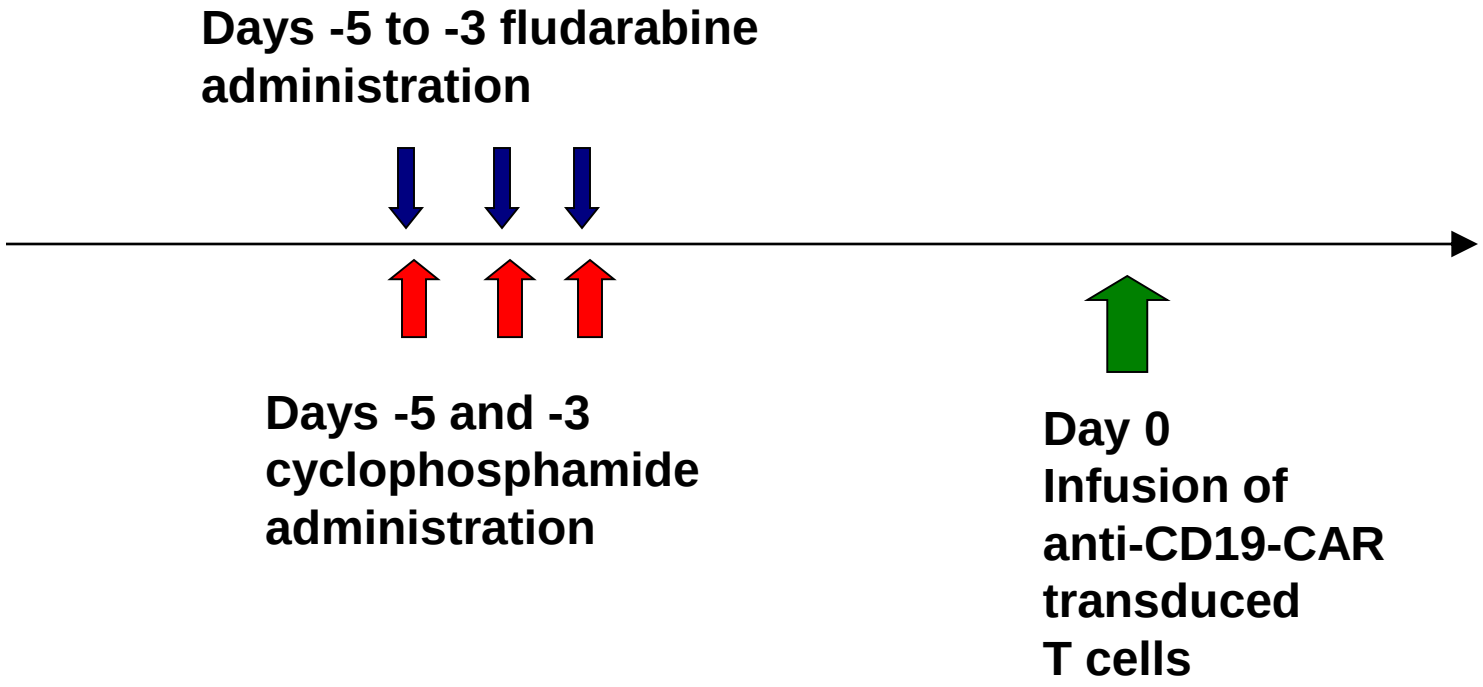
- Aside from this death, toxicities resolved within 3 weeks after the cell infusions.

- Prominent toxicities included fever, hypotension, elevated creatinine, and neurological toxicity including confusion and aphasia.

- Aside from the patient who died, 4 patients required vasopressors, and 2 patients required mechanical ventilation.

- 3 patients had aphasia that was followed by other neurological toxicities such as confusion, cranial nerve paresis, and generalized myoclonus.

Treatment plan 2: anti-CD19 CAR protocol with low-dose chemotherapy



Cyclophosphamide: 300 mg/m^2 daily for 3 days

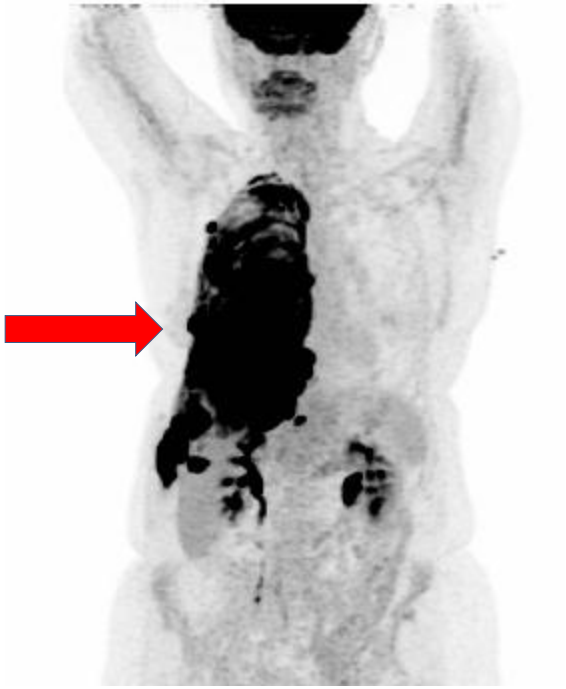
Fludarabine: 30 mg/m^2 daily for 3 days

Summary of anti-malignancy responses in low- dose chemotherapy patients

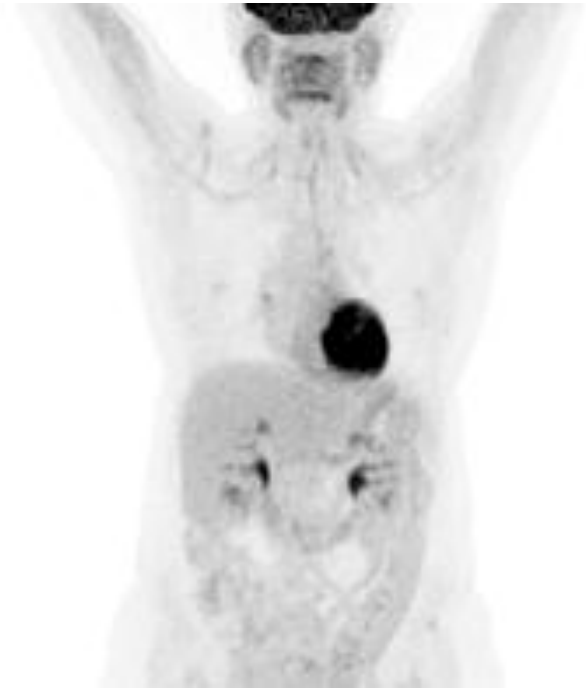
- 9 patients treated
- 8 with DLBCL, 1 with follicular lymphoma
- 8 of 9 patients had chemo-refractory lymphoma or lymphoma that relapsed after autologous stem cell transplantation
- 2 patients obtained CRs, 4 patients obtained PRs, 3 patients had progression of lymphoma

Patient 2 obtained a PR of chemotherapy-refractory triple-hit DLBCL after infusion of anti-CD19 CAR T cells

Before treatment



6 months after treatment



Resolution of a large malignant pleural effusion and lymphoma masses

Grade 3 and 4 non-hematologic toxicities experienced by patients receiving low-dose chemotherapy plus anti-CD19 CAR T cells

Patient	Grade 3 and 4 non-hematologic toxicities
1	Hypotension
2**	Fever
3	Encephalopathy (somnolence)
4**	Aphasia, Tachycardia
5	Aphasia
6	Hyponatremia
7	Hypokalemia
8	Transaminitis, myelitis (visual impairment)
9	PTT increase

**Compassionate exemption

Summary of low-dose chemotherapy regimen

- **We have demonstrated anti-lymphoma activity of anti-CD19 CAR T administered after low-dose chemotherapy.**

- **No patients receiving anti-CD19 CAR T cells after low-dose chemotherapy have required ICU admission or vasopressors.**

- **With our current low-dose chemotherapy regimen, the most troubling problem is short-term neurological toxicity that generally resolves within 4 to 14 days.**

- **The most common neurological toxicities that we have seen are dysphasia, ataxia, and tremor.**

Conclusions and questions on high-dose versus low-dose chemotherapy preceding CAR T-cell infusions

- **Compared to our previous anti-CD19 CAR treatment protocol, preliminary results indicate that lowering the chemotherapy dose reduces overall toxicity.**

- **In mice, host lymphocyte depletion increases inflammatory cytokine production by adoptively-transferred T cells.**

- **Does decreasing chemotherapy dose lead to lower serum levels of inflammatory cytokines after CAR T-cell infusions?**

- **Does reducing chemotherapy dose improve the efficacy to toxicity ratio?**

- **Does reduction of chemotherapy allow safe administration of a higher dose of CAR T cells?**

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