INTERVIEW

David L Porter, MD

Dr Porter is the Jodi Fisher Horowitz Professor of Leukemia Care Excellence and Director of Blood and Marrow Transplantation at the Abramson Cancer Center at the University of Pennsylvania Health System in Philadelphia, Pennsylvania.

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Select Excerpts from the Interview

Tracks 1-6

DR LOVE: Would you talk about the principles of chimeric antigen receptor (CAR) T-cell therapy?

DR PORTER: The advent of lentiviral vectors has allowed us to efficiently deliver genetic material into T cells. Another major advance in CAR T-cell therapy is the ability to expand T cells ex vivo to numbers that are clinically meaningful. The development of anti-CD3/CD28-coated magnetic beads, to engage the T-cell receptor with appropriate costimulation, allowed the activation and expansion of T cells in culture.

The inclusion of new signaling molecules in the CAR causes robust proliferation and improves the antitumor activity of the T cells. These signaling molecules provide a survival signal to the T cells so they can persist for a long time. One of the most interesting recent findings is that genetically modified T cells can be infused into a patient and can expand by 1,000-fold or more, with long-term persistence.

It has been known for a long time that you could redirect the target of an autologous T cell. Preclinical studies showed that the genetically modified redirected T cells could kill cancer cells expressing the appropriate target.

Experiments in mice revealed that these modified T cells could undergo robust proliferation. Various iterations of the CAR were tested, and we were able to optimize the signaling and cosignaling domains. Inclusion of the 4-1BB costimulatory domain was shown to make the CAR more potent. This technology was also shown to be safe. The next step was to test it in clinical trials.

DR LOVE: Would you discuss the available clinical trial data with CAR T-cell therapy for patients with chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL)?

DR PORTER: Our group at the University of Pennsylvania has treated more than 70 cases of CLL and ALL. The CAR we have engineered targets CD19, a molecule expressed on the surface of most B-cell cancers. T cells are collected by leukapheresis and transduced with a lentivirus encoding the CAR construct. The genetically modified cells are expanded and activated in the laboratory. Patients are infused with the CAR-modified T cells in an outpatient setting.

The first 3 patients with CLL to whom we administered CAR T-cell therapy had incredibly rapid antitumor responses. All of the patients had heavily pretreated, extensive disease (Porter 2011). Although we expected this technology would work, we were surprised by the potency of the therapy.

At ASH 2013 we reported the updated results of a pilot trial of 14 patients with relapsed/refractory CLL. The overall response rate was 57%, with half of those being complete responses and half partial responses (Porter 2013a; [1.1]). Even the partial responses were remarkable and clinically meaningful. A number of patients had complete clearance of CLL from their blood and bone marrow. Patients with bulky adenopathy slowly improve over time.

The CLL trials are ongoing and early in development. However, 2 patients we had initially seen are in remission after about 3.5 years. They still have genetically modified T cells detectable in their blood and bone marrow. The follow-up on the other patients in remission ranges from about 3 to 18 months.

We have also treated relapsed/refractory ALL in adults and children who have a dismal prognosis. All 5 of the evaluable adult patients achieved a complete remission. We have a collaboration with Steve Grupp from Children's Hospital, who has administered CAR-modified T cells to pediatric patients with relapsed/refractory disease.

Many of the patients on the study had experienced relapse after allo-SCT. The complete remission rate was 82% with the CAR T-cell therapy (Grupp 2013; [1.2]). This has no precedent in relapsed/refractory ALL. Several of these patients have experienced relapse, but the ongoing complete remission rate is more than 50%, which is remarkable.

DR LOVE: What kinds of complications have you seen with CAR T-cell therapy?

DR PORTER: Delayed cytokine release syndrome (CRS) is observed in all responding patients between 4 and 20 days after infusion of CAR-modified T cells. This syndrome starts with febrile episodes, which can last a few days with fevers that are quite high. Patients have to be carefully evaluated to ensure there is no infection. Nausea, anorexia and in some cases severe myalgia and arthralgia can also occur (Porter 2013a). As it progresses with time, patients may develop hypotension and hypoxia, which may require intensive care.

1.1

Efficacy and Safety of CAR-Modified T Cells Directed Against CD19 in Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)

Efficacy	n = 14	Response in blood, marrow, nodes
Overall response rate	8 (57%)	NED
Complete response*	4 (28.5%)	PR (n = 2)
Partial response (PR)	4 (28.5%)	Blood, marrow NED, nodes PR (n = 2)

Select adverse events

- Cytokine release syndrome (CRS) in all responding patients
  - Characterized by high fever, myalgia, nausea, hypotension, hypoxia
  - Rapidly reversed with steroids (n = 1) or tocilizumab (n = 4)
- Tumor lysis syndrome coincident with T-cell expansion
- Hepatotoxicity (reversible, Grade 3/4 in 4 responding patients)
- Renal toxicity (Grade 3/4 in 4 patients)

Conclusions: CTL019 cells can undergo robust in vivo expansion and can persist for at least 3 years. CTL019 therapy is associated with a significant CRS that responds rapidly to anticytokine treatment. CTL019 cells can induce potent and sustained responses for patients with advanced, relapsed and refractory CLL regardless of p53 mutation status.

NED = no evidence of disease
* Minimal residual disease-negative

Porter DL et al. *Proc ASH* 2013a;**Abstract 4162**.

1.2

CAR T Cells Targeting CD19 (CTL019) Produce Significant In Vivo Proliferation, Complete Responses and Long-Term Persistence in Children and Adults with Relapsed, Refractory Acute Lymphoblastic Leukemia (ALL)

Response	n = 17
Complete response (CR)	82%
Ongoing bone marrow CR	64.7%

- CT019 cells undergo robust in vivo expansion and can persist for 15 months or longer in patients with relapsed ALL.
- These cells can induce potent and durable responses in patients with relapsed/refractory ALL.

Grupp SA et al. *Proc ASH* 2013;**Abstract 67**.

CRS is associated with high levels of IL-6 and can be rapidly reversed with the IL-6 receptor antagonist tocilizumab (1.1, 1.3). The toxicities associated with CAR T-cell therapy can be severe but in all cases have been reversible. We have not had any deaths related to the therapy.

Tumor lysis syndrome is observed in many cases and occurs concurrently with CRS. Both syndromes occur at the time of peak expansion of the genetically modified T cells. I believe they're both related to rapid T-cell proliferation. Complications from the tumor lysis syndrome can be prevented by administering a xanthine oxidase inhibitor such as allopurinol. Rasburicase is effective in treating the hyperuricemia associated with tumor lysis syndrome.

1.3

Managing Cytokine Release Syndrome (CRS) Associated with Novel T-Cell-Engaging Therapies

"CRS correlates with both toxicity and efficacy in patients receiving novel T cell-engaging therapies like CAR-modified T cells. Elevations in effector cytokines and cytokines associated with hemophagocytic lymphohistiocytosis or macrophage activation syndrome, such as interleukin (IL)-10 and IL-6, may be markedly elevated. Corticosteroids may control some of these toxicities. However, their potential to block T-cell activation and abrogate clinical benefit is a concern. One approach developed targets IL-6, a prominent cytokine in CRS, using the IL-6R antagonist tocilizumab."

Maude SL et al. *Cancer J* 2014;20(2):119-22.

DR LOVE: Is there a reason this therapy is not effective in some patients?

DR PORTER: We don't understand why this therapy works for some patients and not for others. We are currently trying to identify which patients may benefit. A randomized Phase II, dose-optimization study of CAR-modified T cells in patients with relapsed/refractory CLL is currently ongoing. A preliminary analysis of the results reported at ASH 2013 suggests that there is no dose-response or dose-toxicity effect (Porter 2013b; [1.4]).

We have ongoing studies investigating different factors of the patients' immune systems. The T-cell function of patients whose disease does and does not respond are being compared. As of now we have not been able to identify any factors that would predict which patients would experience response. ■

1.4

Correlation between CTL019 Dose and Response or Toxicity in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Response (n)	High dose (5×10^8) cells	Low dose (5×10^7) cells
Major response (CR + PR)	4	3
No response	5	6
Toxicity (n)	**High dose (5×10^8) cells**	**Low dose (5×10^7) cells**
CRS	5	6
No CRS	4	3

CR = complete response; PR = partial response; CRS = cytokine release syndrome

Porter DL et al. *Proc ASH* 2013b;**Abstract 873**.

SELECT PUBLICATIONS

Grupp S et al. **T cells engineered with a chimeric antigen receptor (CAR) targeting CD19 (CTL019) produce significant in vivo proliferation, complete responses and long-term persistence without GVHD in children and adults with relapsed, refractory ALL.** *Proc ASH* 2013;**Abstract 67**.

Maude SL et al. **Managing cytokine release syndrome associated with novel T cell-engaging therapies.** *Cancer J* 2014;20(2):119-22.

Porter DL et al. **Chimeric antigen receptor modified T cells directed against CD19 (CTL019 cells) have long-term persistence and induce durable responses in relapsed, refractory CLL.** *Proc ASH* 2013a;**Abstract 4162**.

Porter DL et al. **Chimeric antigen receptor therapy for B-cell malignancies.** *J Cancer* 2011;2:331-2.