T Cells Engineered with CAR Targeting CD19 in Patients with Relapsed/Refractory ALL
CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they’re aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on chimeric antigen receptor T-cell therapy for leukemia and lymphoma from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Develop an understanding of the mechanism of action of chimeric antigen receptor T-cell therapy, and evaluate the emerging efficacy and safety data with this therapeutic approach under evaluation in the front-line and relapsed/refractory settings for B-cell lymphoma and leukemias.
- Evaluate the benefits and risks of the addition of gemtuzumab ozogamicin to standard chemotherapy and of other emerging agents such as novel FLT3 inhibitors or hypomethylating agents for the treatment of acute myeloid leukemia.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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No real or apparent conflicts of interest to disclose.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: May 2014
Expiration date: May 2015
To go directly to slides and commentary for this issue, [click here](#).

On this final issue of our review of select key papers presented at the American Society of Hematology annual meeting, we focus on a handful of fascinating early clinical reports on CART and a smattering of what’s new in AML.

**CART clinical trial data**

Although we heard about the seemingly miraculous effects of this novel therapeutic approach in 2012 in Atlanta, New Orleans was the true coming out party for CART-based approaches, specifically those targeting CD19. Led by the powerhouse team at the University of Pennsylvania, which includes Dr David Porter, we were treated to numerous fascinating presentations that have generated great excitement and enthusiasm.

Since ASH I have been fortunate enough to interview Dr Porter on 2 occasions ([click for audio](#)), and it is impossible to hear about this dramatic story without getting goose bumps.

The concept behind Penn’s CART-based approach is intriguing. Patients undergo leukapheresis, after which their T-cells are transduced with a lentivirus encoding an anti-CD19 single-chain variable fragment linked to 4-1BB and CD3-ζ signaling domains. The genetically modified cells are then expanded ex vivo, and soon after a course of lymphocyte-depleting chemotherapy they are then reinfused into the patient where, as documented previously and in new reports at ASH, they expand (up to 10,000-fold), persist functionally (beyond 3 years) and exert a direct antitumor effect.

Early efforts by the group have focused on very advanced chronic lymphocytic leukemia (CLL) and B-cell acute lymphoblastic leukemia (ALL), and although they hoped to see some discernible benefit in early testing, as related by Dr Porter, the initial clinical responses were stunning in rapidity and depth. Much of this work was updated and expanded on in New Orleans. Dr Stephan Grupp [presented longer follow-up outcomes](#) from 17 adults and children with relapsed/refractory ALL revealing that 82% achieved a complete response (CR). Similarly, Dr Porter [provided an update](#) from their Phase I study in which 8 of 14 patients with extensively pretreated CLL had objective responses, including 4 patients with CRs, none of whom have yet experienced
relapse. He also unveiled data from their dose-finding randomized Phase II study demonstrating that 7 of 18 patients responded, including 3 CRs, with no correlation between dose and outcome or toxicity.

Perhaps the highlight of these presentations, at least in my mind, was an impressive set of scans that Dr Porter displayed from a patient with del(17p) CLL treated on their original pilot study. Amazingly, 3 months after receiving the CART infusion this individual, whose disease had progressed through 10 prior therapies, including ibrutinib and radiation therapy, was pretty much disease free in peripheral blood and bone marrow.

In discussing this work with Dr Porter, I was eager to learn more about the profound and rapid tumor lysis/cytokine release syndrome (CRS) that has been described with this therapy. I was wide-eyed as he detailed the team’s early experiences with this scary complication that generally occurred within the first few weeks of treatment at the peak of initial T-cell expansion and initially led to life-threatening multiorgan failure. What was perhaps most compelling was that the team was able to quickly determine that the key cytokine causing this syndrome was IL-6, and they were able to successfully intervene with a novel IL-6 receptor antibody approved for rheumatoid arthritis (tocilizumab).

Penn is not alone at the forefront of this research, and at ASH the Memorial group also reported activity with a slightly different anti-CD19 CAR platform across several diseases. In high-risk CLL, Dr Jae Park presented preliminary data from a Phase I study evaluating this approach as consolidation after up-front rituximab-chemotherapy. While the data set was quite small — 8 patients with 2 CRs and 2 partial responses — it provides an important proof of principal that ultimately may allow some patients with CLL to receive a short-term treatment that will lead to prolonged tumor control. Relevantly, the study results suggest greater benefit in patients with lower tumor burden, and Dr Porter believes that an important future strategy will be initial cytoreduction, particularly with novel B-cell inhibitors like ibrutinib, followed by an attempt at cure with CART.

Memorial’s Dr Marco Davila also reported on CAR therapy as a bridge to allotransplant in patients with B-cell ALL, including those with Philadelphia chromosome-positive disease. Importantly, responses were rapid, occurring as early as 7 to 14 days, CRS was manageable and 10 of 12 patients with detectable disease before CAR therapy became minimal residual disease-negative. Four patients went on to allotransplant with 5 more being prepped for it.

The NCI, too, is very involved in this field, and at ASH they provided us with more data on the use of this technology in ALL as well as our first look at it in B-cell lymphomas, where 5 of 8 patients with chemotherapy-refractory diffuse large B-cell lymphoma or primary mediastinal B-cell lymphoma experienced objective tumor responses.

The next step for this fascinating and innovative treatment strategy is to not only obtain more data but also to investigate the feasibility and reproducibility of doing this on a larger-scale basis.
**AML: Life beyond 3 plus 7**

The dismal current landscape of this important cause of mortality is reflected by the fact that the only compound approved for this disease in the last 20 years, gemtuzumab ozogamicin (GO), was removed from the market by the FDA 4 years ago due to toxicity concerns.

As such, for far too long conversations about AML management have revolved around optimal induction and consolidation chemotherapy doses and schedules and the role for various transplant strategies. However, the rapidly emerging translational and related clinical science that permeates ongoing AML research has many optimistic that brighter days are ahead (click for summary slides of studies discussed below).

One of the more talked about areas is management of the 30% of patients with FMS-like tyrosine kinase 3 (FLT3) mutations, and in the Big Easy Dr Jorge Cortes presented a provocative study on the effects of the as yet unapproved FLT3 inhibitor quizartinib. One of the proposed benefits of this agent is that it is more specific for the target than tyrosine kinase inhibitors such as sorafenib, which is sometimes employed off label when no other alternatives exist. In this Phase II study using lower doses of quizartinib in 76 patients, a 47% CR rate with acceptable toxicities was reported. All eyes are on the ongoing Phase III study evaluating this compound in hopes that it may end up as a useful tool in practice.

The MD Anderson group also reported on SGI-110 — a novel molecule that combines decitabine with guanosine to produce a longer half-life and potentially higher areas under the curve than decitabine. Importantly, in this Phase II study this subcutaneously administered hypomethylating agent resulted in an encouraging preliminary objective response rate of 53% in elderly patients with treatment-naïve AML. Dr Hagop Kantarjian and his group at MD Anderson are interested in doing a study comparing this agent to conventional decitabine or azacitidine.

Because activating KIT mutations are present in 25% to 30% of patients with core binding factor (CBF) AML, it has been hypothesized that KIT inhibition might provide therapeutic benefit. In this regard, the CALGB reported on a single-arm trial evaluating the addition of dasatinib to induction chemotherapy in patients with molecular confirmation of CBF AML. Reported at ASH, the trial resulted in an encouraging CR rate of 92% in 59 evaluable patients, but many are reserving judgment about this approach until further follow-up is available.

Given its activity in a multitude of hematologic cancers, it should probably come as no surprise that lenalidomide is also being evaluated in AML. Significantly, preliminary results look encouraging with a CR rate of 43% in 37 elderly patients over age 70 with low-dose lenalidomide added to low-dose Ara-C (LDAC). Perhaps even more importantly, a 5-gene molecular signature has been identified that appears highly predictive of treatment response with 87% overall accuracy.

Additionally, although the previously mentioned anti-CD33 antibody-drug conjugate GO is no longer available, at ASH we saw data reinforcing its evidence-based benefit most
specifically for patients with CBF AML. Described in a meta-analysis, a pediatric study and a longitudinal analysis of trials of the UK MRC/NCRI group, these results all point to a modest advantage with limited toxicity. Whether GO will make it back into the clinic, however, remains unclear.

Finally, in terms of the FDA and AML, one of the more interesting and positive recent developments from the agency has been the 2012 implementation of the “Breakthrough Therapy” designation pathway, which fast-tracks promising agents in diseases with important unmet needs. Over the past year on our CME programs we have discussed many exciting oncology compounds that have earned this designation, and just 2 weeks ago we saw this novel pathway in action as the second-generation ALK inhibitor ceritinib was granted accelerated approval in ALK-positive non-small cell lung cancer based on the results of a single-arm, open-label clinical trial enrolling 163 patients.

Last fall, the selective and potent polo-like kinase (PLK) inhibitor volasertib became the only “AML drug” to join this short “Breakthrough” list. Volasertib inhibits PLK1 — the best characterized of the 5 known human PLKs and a critical enzyme regulating mitosis — resulting in cell cycle arrest and ultimately cell death (apoptosis). At ASH 2012 a randomized Phase I/II trial reported an impressive response rate advantage when the agent was added to LDAC in patients not eligible for intensive induction. These encouraging results led to the ongoing Phase III POLO-AML-2 trial with a similar randomization in patients age 65 or older with previously untreated AML not eligible for intensive induction. Although the future of this interesting agent is unclear, it seems plausible that in the next few years AML will join the other myeloid cancers in seeing the documented benefit of important new and clinically useful treatment strategies based on the evolution of understanding the underlying disease biology.

This concludes our ASH review series. If you’re heading to Chicago this month, join us at the end of each day for a series of evening symposia as we review what’s happening in lung cancer, gastrointestinal cancers, non-Hodgkin lymphoma/multiple myeloma and HER2-positive breast cancer.

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T Cells Engineered with CAR Targeting CD19 in Patients with Relapsed/Refractory ALL

Presentation discussed in this issue

Grupp SA 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.

Slides from a presentation at ASH 2013 and transcribed comments from recent interviews with Hagop M Kantarjian, MD (1/29/14) and David L Porter, MD (3/3/14)

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

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

- CARs combine a single-chain variable fragment (scFv) of an antibody with intracellular signaling domains into a single chimeric protein.
- A previous study of CTL019 cells expressing a CAR with intracellular activation and costimulatory domains demonstrated that (NEJM 2013;368:1509):
  - Infusion of these cells results in 100 to 100,000 times in vivo proliferation, durable antitumor activity and prolonged persistence in patients with B-cell tumors, including 1 sustained complete remission (CR) in a patient with acute lymphocytic leukemia (ALL).
- **Study objective:** To report on longer follow-up outcomes of patients with relapsed/refractory ALL who have undergone infusion of CTL019 cells.


Study Methods

- 20 patients with relapsed/refractory CD19-positive ALL underwent treatment.
  - Children (n = 16); adults (n = 4)
- All patients received an infusion of T cells that had been lentivirally transduced with a CAR composed of anti-CD19 scFv/4-1BB/CD3\(\zeta\) and activated/expanded ex vivo with anti-CD3/anti-CD28 beads.
- 17 of 20 patients received lymphodepleting chemotherapy the week prior to CTL019 infusion.
- 11 patients had relapsed ALL after previously undergoing allogeneic stem cell transplantation (allo-SCT).
- T cells were collected from patients regardless of prior SCT status.

Grupp SA et al. Proc ASH 2013;Abstract 67 (abstract only).
Study Methods (Continued)

- No graft-versus-host disease (GVHD) or GVHD treatment in the 6 months after allo-SCT was allowed.
- The targeted T-cell dose ranged from $10^7$ to $10^8$ cells/kg with a transduction efficiency (TE) of 11% to 45%.
- On the adult protocol, the target dose was $5 \times 10^9$ total cells split over 3 days with a TE of 6% to 31%.
- A median of $3.7 \times 10^6$ CTL019 cells/kg (0.7 to $18 \times 10^6$/kg) were infused over 1 to 3 days.
- Lymphodepleting chemotherapy varied, with most patients receiving a cyclophosphamide-containing regimen the week prior to CTL019 infusion.

Grupp SA et al. Proc ASH 2013;Abstract 67 (abstract only).

Baseline Characteristics

- 16 children of median age 9.5 years (5-22) and 4 adults of median age 50 years (26-60) with CD19-positive ALL received treatment.
- 1 child had T-cell ALL aberrantly expressing CD19.
- 14 of 16 pediatric patients had active disease or minimal residual disease (MRD) after chemotherapy on the day prior to CTL019 cell infusion, and 2 were MRD-negative.
- 3 of the 4 adults had active disease prior to lymphodepleting chemotherapy, and 1 was in morphologic CR.

Grupp SA et al. Proc ASH 2013;Abstract 67 (abstract only).
Response Rates

<table>
<thead>
<tr>
<th>Response</th>
<th>n = 17*</th>
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<tbody>
<tr>
<td>CR</td>
<td>82%†</td>
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<tr>
<td>With ongoing bone marrow (BM) CR</td>
<td>64.7%</td>
</tr>
<tr>
<td>With no response</td>
<td>17.6%</td>
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* Evaluable patients
† Includes the patient with CD19-positive T-cell ALL
- Median follow-up: 2.6 months
- Patients pending evaluation (n = 3)
- Three patients who achieved a CR at 1 month have experienced relapse
  - One had CD19-negative ALL


Clinical Outcomes

- Although T cells collected from the 11 patients who experienced relapse after allo-SCT were generally 100% of donor origin, no GVHD has been seen.
- Persistence of CTL019 cells detected by flow cytometry and/or quantitative PCR in patients with ongoing responses continued for 1 to 15 months after infusion, resulting in complete B-cell aplasia during the period of CTL019 persistence.
- Patients have been treated with IVIg without any unusual infectious complications.
- One child who achieved a CR subsequently developed myelodysplastic syndrome with a new trisomy 8 abnormality and has undergone SCT.
- One child who developed a single leukemia cutis lesion at 6 months still has BM MRD-negative status.

Treatment-Related Adverse Events

- All patients with responsive disease developed some degree of delayed cytokine release syndrome (CRS), concurrent with peak T-cell expansion.
  - Manifested by fever, myalgia, nausea and anorexia
- Some patients experienced hypotension and hypoxia.
- Treatment for CRS was required for hemodynamic or respiratory instability in 7 of 20 patients.
- CRS was rapidly reversed in all cases with the IL-6 receptor antagonist tocilizumab (7 patients), which was combined with corticosteroids in 4 cases.

Grupp SA et al. Proc ASH 2013;Abstract 67 (abstract only).

Treatment-Related Adverse Events (Continued)

- Cytokine analysis showed marked increases from baseline values of IL-6 and interferon gamma (both up to 1,000 times) and the IL-2 receptor, with mild or no significant elevation in systemic levels of tumor necrosis factor alpha or IL-2.
- There were no infusion-related toxicities of Grade >2 intensity.
- However, 5 patients developed fevers within 24 hours of infusion and did not receive the planned subsequent infusions of CTL019 cells.

Grupp SA et al. Proc ASH 2013;Abstract 67 (abstract only).
Author Conclusions

- CTL019 cells are T cells genetically engineered to express an anti-CD19 scFv coupled to CD3ζ signaling and 4-1BB costimulatory domains.
- These cells can undergo robust in vivo expansion and can persist for ≥15 months in patients with relapsed ALL.
- CTL019 therapy is associated with a significant CRS that responds rapidly to IL-6-targeted anticytokine treatment.
- This approach has promise as salvage therapy for patients with relapsed disease after allo-SCT, and the collection of tolerized cells from the recipient appears to have a low risk of GVHD.
- CTL019 cells can induce potent and durable responses for patients with relapsed/refractory ALL.
- Multicenter trials are being developed to test this therapy in ALL in the Phase II setting.


Investigator Commentary: T Cells Engineered with CAR Targeting CD19 in Patients with Relapsed/Refractory ALL

This is an exciting new field of reengineering T cells. Several studies of CAR T cells have reported that most patients — particularly those with ALL — achieve complete remissions, some of which are durable. In this study, of the 17 evaluable patients with ALL who received CAR T cells, 14 (82%) achieved a CR. However, the delayed CRS experienced by patients who respond is of concern. This phenomenon is believed to result from a reaction to the T cells killing the leukemia cells. Within a week or 2 of receiving treatment, patients develop fever, bone aches, muscle aches, nausea/vomiting and anorexia. With appropriate management and early intervention, particularly with the use of steroids and anti-IL-6 receptor antibody, CRS symptoms can be alleviated.

This approach is exciting, but it needs to be further evaluated in terms of applicability and side effects.

*Interview with Hagop M Kantarjian, MD, January 29, 2014*
These investigators previously published results on the potent activity of CAR T cells in 2 patients with relapsed or refractory ALL (NEJM 2013;368(16):1509). The current study is the largest experience so far with genetically modified T cells in ALL. The most important aspect of the study is the high, remarkable response rate observed in children and adults — 82% achieved a CR. Most of the CRs had no evidence of MRD, indicating that they were deep and significant. Of note, many of the patients on the study had experienced relapse after allo-SCT. In all cases, either before or after SCT, the patients essentially had no effective treatment options.

Another important aspect of this study is that it detailed CRS extremely well. Many investigators using CAR T cells have identified CRS as an issue. Dr Grupp's group was the first to recognize that IL-6 levels are high in these patients and that intervention with an anti-IL-6 receptor antagonist, tocilizumab, works in a matter of hours to reverse critical and life-threatening side effects. Finally, a unique finding is the description of long-term persistence of the CAR T cells. This is crucial due to the possibility that persistence is necessary for ongoing disease control. I believe that therapy with CAR T cells has the potential to revolutionize treatment of relapsed ALL after the failure of allo-SCT.

Interview with David L Porter, MD, March 3, 2014