642. CLL: THERAPY, EXCLUDING TRANSPLANTATION: POSTER III | NOVEMBER 15, 2013

Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019 cells) Have Long-Term Persistence and Induce Durable Responses In Relapsed, Refractory CLL

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Abstract

Background

Chimeric antigen receptors (CARs) combine the antigen recognition domain of an antibody with intracellular signaling domains into a single chimeric protein. CD19 is an ideal target for CARs since expression is restricted to normal and malignant B cells. Inclusion of the CD137 (4-1BB) signaling domain results in potent antitumor activity and in-vivo persistence of anti-CD19 CAR-modified T cells in mice. Lentiviral transduction into T cells facilitates strong surface expression of the CAR. We reported anti-tumor activity of CAR-modified autologous T cells targeted to CD19 (CTL019 cells) in 3 patients (pts) with CLL with relatively short follow up (Porter, et al NEJM 2011; Kalos et al Sci Trans Med 2011). We now report on outcomes and longer follow up from our pilot study treating 14 pts with relapsed, refractory CLL.

Methods

Autologous T cells collected by leukapheresis were transduced with a lentivirus encoding anti-CD19 scFv linked to 4-1BB and CD3-ζ signaling domains. Gene-modified T cells were expanded and activated ex-vivo by exposure to anti-CD3/CD28 beads. Pts had to have relapsed or persistent disease after at least 2 previous treatments (1 prior therapy for patients with p53 mutation) and progressed at least within 2 years of their last therapy. All pts received lymphodepleting chemotherapy ending 3-5 days before T cell infusion. The target dose of cells was 5 x 10^9 mononuclear cells with an expected transfection efficiency of 10-40% (total CTL019 dose $5x10^8$ – 2 x 10^9 total cells). Cell infusions were planned over 3 days (10% on day 1, 30% of day 2, and 60% on day 3) but were held for fevers or other toxicity.

Results

14 patients were treated on this pilot study including 12 men and 2 women with a median age of 67 (51-78). Pts had received a median of 4 prior therapies (1-10) and 6 pts had a mutation of p53. All pts had active disease at the time of CTL019 cell infusion. Lymphodepleting chemotherapy was Fludarabine/cyclophosphamide (3), pentostatin/cyclophosphamide (5), or bendamustine (6). A median of 7.5 x 10^8 total cells (range 1.7-50), corresponding to 1.4 x 10^8(range 0.14-5.9) genetically modified cells were infused over day 0, 1 and 2.

There were no infusional toxicities >grade 2 though 6 pts developed fevers within 24 hrs of infusion #1 (3) or #2

and 16 mo (5-35) for the 8 responding pts. 3 patients (21%) achieved a CR (follow-up 11, 34, and 35 mo), 5 (36%) achieved a PR (med follow up 11 mo, range 5-27 mo) and 6 (43%) had no response, for an overall major response rate of 57%. 2 of 5 pts with a PR progressed 4 mo after infusion with CD19+ CLL, and no patient with a CR has relapsed.

Comparing responders to non-responders, there has been no association between response and patient age (66 vs 67 yrs), number of prior therapies (median 4 each), cell dose (7.5 vs 11.5 x 10^8MNC), or p53 mutation (3/8 vs 3/6, p>0.9), implying that within the dose ranges studied, there is no obvious dose:response relationship.

All responding pts developed a delayed cytokine release syndrome (CRS), concurrent with peak T cell expansion, and was manifested by fever, and variable degrees of nausea, anorexia, myalgias, and transient hypotension and hypoxia. Detailed cytokine analysis showed marked increases from baseline values of IL6, IFN-γ, and IL2R, while no significant elevation in systemic levels of TNFα or IL2 were observed. The CRS required intervention in 5 patients. Treatment was initiated for hemodynamic or respiratory instability and was rapidly reversed in all cases with corticosteroids in 1 pt and the IL6-receptor antagonist tocilizumab (4 pts); 3 of these 4 pts also received 1 or 2 doses of corticosteroids. Persistence of CTL019 cells has been detected by flow cytometry in all 6 pts with ongoing responses 5-35 months after infusion, and all patients have sustained B cell aplasia without any unusual infectious complications.

Conclusions

CTL019 cells are autologous T cells genetically engineered to express an anti-CD19 scFv coupled to 4-1BB/CD3-ζ signaling domains. These cells can undergo robust in-vivo expansion and can persist for at least 3 yrs. CTL019 therapy is associated with a significant CRS that responds rapidly to anti-cytokine treatment. CTL019 cells can induce potent and sustained responses (8/14) for patients with advanced, relapsed and refractory CLL regardless of p53 mutation status.

Disclosures:

Porter:*Novartis:* Patents & Royalties, Research Funding; *Genentech:* Spouse employment, Spouse employment Other. **Off Label Use:** CTL019 cells to treat CLL. **Kalos:***Adaptive biotechnologies:* Member scientific advisory board , Member scientific advisory board Other; *Novartis corporation:* CART19 technology, CART19 technology Patents & Royalties. **Grupp:***Novatis:* Research Funding. **Lledo:***Novartis:* Research Funding. **Chew:***Novartis:* Patents & Royalties. **Zheng:***Novartis:* Patents & Royalties. **Levine:***Novartis:* cell and gene therapy IP, cell and gene therapy IP Patents & Royalties. **June:***Novartis:* Patents & Royalties, Research Funding.

Topics: cd19 antigens, chimeric antigen receptors, chronic lymphocytic leukemia refractory, t-lymphocytes, brachial plexus neuritis, follow-up, infusion procedures, fever, adrenal corticosteroids, chemotherapy regimen

Author notes

* Asterisk with author names denotes non-ASH members.