Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Nat Rev Clin Oncol. Author manuscript; available in PMC 2019 January 10.

Published in final edited form as:

Nat Rev Clin Oncol. 2014 December ; 11(12): 685–686. doi:10.1038/nrclinonc.2014.190.

Treatment of aggressive lymphomas with anti-CD19 CAR T cells

Christopher A. Klebanoff, **Tori N. Yamamoto**, and **Nicholas P. Restifo**

Center for Cancer Research, Surgery Branch, Immunotherapy Section, 10 Center Drive, Building 10/CRC, Room 3 West-5816, Bethesda, MA 20892, USA.

Abstract

Adoptive immunotherapy using T cells genetically engineered to express a chimeric antigen receptor that targets CD19, a B-cell differentiation antigen, has demonstrated impressive efficacy in a range of B-lymphoid malignancies. The latest results demonstrate the potential of this approach in patients with chemotherapy-refractory diffuse large B-cell lymphoma.

Adoptive cell-transfer (ACT) therapy, which involves the *ex vivo* expansion and reinfusion of tumour-reactive T cells, is emerging as a potential curative treatment for patients with advanced-stage cancer. The ability of ACT to mediate durable complete responses was first demonstrated in patients with melanoma who received surgically-obtained, *ex vivo* expanded tumour-infiltrating T lymphocytes.[1] The capacity to genetically engineer T cells to stably express antigen receptors that convey antitumour reactivity has greatly simplified the generation of therapeutic T cells, enabling translation of this approach to a range of solid and haematological cancers. Clinical trials using genetically-retargeted T cells have used both conventional T-cell receptors (TCRs) and chimeric antigen receptors (CARs); the latter combines into a single chimeric protein the recognition domain of a specific antibody against a tumour-associated antigen and an intracellular signalling domain capable of activating T cells. Because CARs target cells independently of the major histo-compatability complex, they offer the possibility for a single genetically-engineered antigen receptor to treat a range of cancer types in a diverse population of patients.

The use of a single antigen receptor to target multiple cancers has been demonstrated with CARs that target CD19, a B-cell lineage differentiation antigen that is expressed on malignant cells in most B-lymphoid malignancies. Kochenderfer and colleagues now report for the first time the successful treatment of patients with diffuse large B-cell lymphoma (DLBCL), the most-common adult lymphoid neoplasm (Figure 1), using the CD19 CAR T-cell approach.[2] This study adds to the list of haematological malignancies refractory to conventional therapies that have been treated successfully with anti-CD19 CAR T cells: these cancers include follicular lymphoma,[3,4] chronic lymphoid leukaemia (CLL),[4,5] and paediatric or adult acute lymphoblastic leukaemia.[6,7]

Correspondence to: C.A.K. klebanoc@mail.nih.gov.

Competing interests

The authors declare no competing interests.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In the study from Kochenderfer and co-workers, nine patients with relapsed or chemotherapy-refractory DLBCL received autologous T cells genetically engineered to express the anti-CD19 CAR.[2] Similar to earlier trials,[3,4] CAR T cells were administered after preconditioning with a non-myeloablative chemotherapy regimen that included cyclophosphamide in combination with fludarabine. The purpose of this regimen was to temporarily deplete host immune-suppressive factors, such as regulatory T cells, and reduce the number of endogenous T cells, which compete for the homeostatic and/or activating cytokines IL-7 and IL-15.[8] In contrast to other studies reported by Kochenderfer,[2,3] patients did not receive the T-cell growth factor IL-2. Furthermore, the dose of transferred cells was reduced approximately 5–50-fold. Both of these changes were introduced in an attempt to simplify the generation and delivery of the therapy, as well as to reduce the frequency of adverse effects. This revised treatment regimen was also tested in six patients with indolent lymphomas and CLL, cancers known to be responsive to anti-CD19 CAR T cells.[3–5]

Four out of seven evaluable patients with DLBCL achieved a complete response consistent with standardized oncological assessment criteria.[2] At the time of publication, three of these complete responses were ongoing, with a response duration ranging from 9–22 months.[2] An additional two patients had a partial response, one of which is ongoing, and a third patient had stabilization of disease.[2] In those patients with indolent lymphomas and CLL, four out of six patients had a complete response and the remaining two patients had a partial response.[2] Collectively, these results confirmed the remarkable ability of anti-CD19 CAR T cells to mediate cancer regression in patients with chemotherapy-refractory disease.

Consistent with previous studies using anti-CD19 CAR T cells,[3–7] immunologically mediated toxic effects were observed. All patients with normal levels of circulating B cells before therapy had complete eradication of these cells following CAR-expressing T-cell infusion, with B-cell depletion lasting for at least 4 months—a predictable effect given the high expression of CD19 on nontransformed B cells.[2] Toxicities occurring primarily within the first 2 weeks of cell infusion were also reported.[2] These adverse effects included temporary symptoms attributable to an exuberant release of T-cell-derived cytokines, such as fever and hypotension.[2] In addition, 20% of patients also experienced transient neurological dysfunction, such as confusion, aphasia, myoclonus, and gait disturbances.[2] The precise aetiology of these neurological symptoms remains unknown, although the presence of CAR-expressing T cells was detected in the cerebral spinal fluid of symptomatic patients. On the basis of a previous report,[6] two patients who experienced severe symptoms attributable to a cytokine-release syndrome were subsequently treated with the anti-IL-6 receptor (IL-6R) antibody tocilizumab;[2] however, neither patient experienced an immediate improvement in symptoms following toclizumab administration, although both patients had complete resolution of their symptoms with supportive care.[2]

As with all small-scale trials, the current study leads to additional and important questions. First, although the frequency of complete responses in this series is impressive, whether they will be durable following a single infusion of T cells (as noted in patients with melanoma who received ACT[1]) will be determined only with extended follow up. Second, the contribution of each of the components of the therapy to the complete responses observed, specifically the type and dose of chemotherapy versus the CAR-transduced T cells, remains

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

unclear. To address this question, future trials will have to either reduce the dose of chemotherapy to a level incapable of mediating meaningful anti-lymphoma responses or patients should be randomized to receive the current standard dose of chemotherapy and CAR T-cell therapy or chemotherapy alone. Third, how the quality of the CAR-expressing T cells can affect the response is also unclear. Preclinical experiments have demonstrated that less-differentiated naive and central memory T-cell subsets mediate superior antitumour responses,[9,10] but prospective data in humans is lacking. Finally, the question of how best to manage CAR-mediated cytokine-release syndromes remains open. Although many groups have adopted the practice of administering anti-cytokine directed therapies such as anti-IL6R antibodies in this setting, whether these drugs enhance clinical improvement or compromise the anticancer response is unclear. Regardless, these data show that the ability of anti-CD19 CAR T cells to induce tumour regression has successfully been extended to include those patients with aggressive B-cell lymphomas.

References

1. Rosenberg SA et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin. Cancer Res. 17, 4550–4557 (2011). [PubMed: 21498393]
2. Kochenderfer JN et al. Chemotherapy- refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J. Clin. Oncol 10.1200/JC0.2014.56.2025 (2014).
3. Kochenderfer JN et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Blood 116, 4099–4102 (2010). [PubMed: 20668228]
4. Kochenderfer JN et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. Blood 119, 2709–2720 (2012). [PubMed: 22160384]
5. Porter DL, Levine BL, Kalos M, Bagg A & June CH Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N. Engl. J. Med. 365, 725–733 (2011). [PubMed: 21830940]
6. Grupp SA et al. Chimeric antigen receptor- modified T cells for acute lymphoid leukemia. N. Engl. J. Med. 368, 1509–1518 (2013). [PubMed: 23527958]
7. Brentjens RJ et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Sci. Transl. Med. 5, 177ra38 (2013).
8. Klebanoff CA, Khong HT, Antony PA, Palmer DC & Restifo NP Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. Trends Immunol. 26, 111–117 (2005). [PubMed: 15668127]
9. Klebanoff CA, Gattinoni L & Restifo N P Sorting through subsets: which T-cell populations mediate highly effective adoptive immunotherapy? J. Immunother. 35, 651–660 (2012). [PubMed: 23090074]
10. Gattinoni L, Klebanoff CA & Restifo N P Paths to stemness: building the ultimate antitumour T cell. Nat. Rev. Cancer 12, 671–684 (2012). [PubMed: 22996603]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

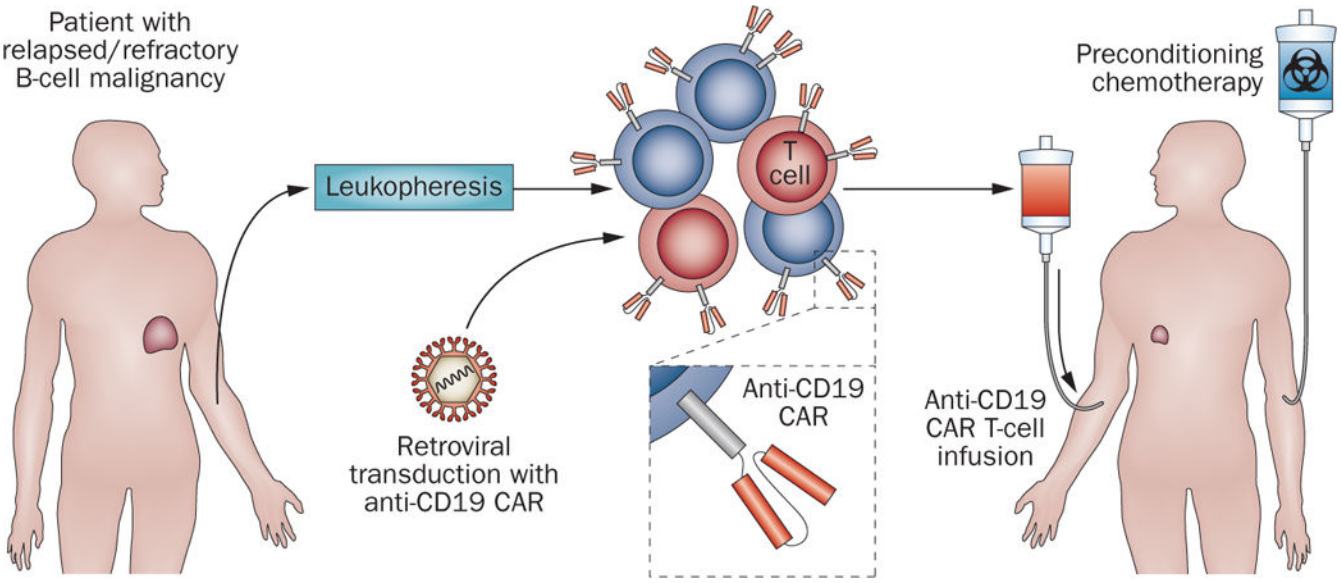

Figure 1 |.

Treatment of patients with B-cell malignancies using anti-CD19 CAR T cells. Patients with relapsed and/or refractory B-cell malignancies expressing the cell-surface protein CD19 can be treated successfully using adoptively transferred autologous T cells genetically engineered to express a CAR recognizing CD19. Abbreviation: CAR, chimeric antigen receptor.