Chimeric Antigen Receptor Therapy for Chronic Lymphocytic Leukemia: What are the Challenges?

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KEYWORDS

• Chimeric antigen receptor • Chronic lymphocytic leukemia • CD19
• Adoptive cell therapy • Cell engineering

KEY POINTS

- Numerous targeted therapies are being developed for patients with chronic lymphocytic leukemia (CLL).
- CAR-modified T cells targeting CD19 expressed by normal and malignant B cells is a unique therapy, and recent results from 4 different trials highlight the dramatic potential of this therapy for patients with relapsed CLL.
- Because adoptive transfer of chimeric antigen receptor–modified T cells is a novel approach to cancer therapy, there are issues for the medical oncologist to consider when evaluating current and future clinical trials for patients with CLL.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the target for numerous new investigational drugs and immunotherapies. Unique among these is the genetic modification of T cells to B-cell antigens through the gene transfer of a chimeric antigen receptor (CAR), which is composed of an antigen-binding component fused to T-cell signaling domains. A patient's own T cells are genetically modified and then adoptively transferred back to the patient to mediate killing of malignant, and normal, B cells. Over the past 10 years, work initiated at the authors' center[1] has transitioned this technology from preclinical models to clinical trials, with evidence of promising results.[2–7] However, there are important details that should be considered when evaluating and comparing the various CAR-modified T cells under study, because this therapy is unlike any traditionally used by the medical oncologist. The goal of this article is to

Disclosures: None.
Funded by: NIH K08CA148821 (MLD) and R01CA138738 (RB).
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Hematol Oncol Clin N Am 27 (2013) 341–353
http://dx.doi.org/10.1016/j.hoc.2012.12.004 **hemonc.theclinics.com**
0889-8588/13/$ – see front matter

describe and evaluate these details, including CAR design, T-cell production and dose, prior conditioning chemotherapy regimens, and tumor burden, and to discuss how they may affect the treatment response in patients with CLL.

RESULTS OF CLINICAL TRIALS

Clinical outcomes of 16 patients with CLL treated with CAR-modified T cells targeted to the B-cell–specific CD19 antigen have recently been reported from 4 trials conducted at various academic medical centers.[2–7] The National Cancer Institute (NCI) reported their results concerning 4 patients with relapsed CLL treated with fludarabine and cyclophosphamide followed by CD19-targeted CAR-modified T cells. These patients, previously treated with an average of 4 chemotherapy regimens, had variable anti-CD19 responses including a complete remission (CR) of greater than 15 months' duration. In addition, several patients developed anticipated B-cell aplasia as a consequence of their treatment and exhibited systemic serum cytokine elevations consistent with robust CAR-modified T-cell activation. Investigators at the University of Pennsylvania (UPenn)[3,4] reported the results of 3 CLL patients treated with CD19-targeted CAR-modified T cells, of whom 2 patients had relapsed disease and 1 patient was chemotherapy-naïve, treated with bendamustine or pentostatin plus cyclophosphamide as conditioning therapy before T-cell infusion. Two of the patients had ongoing CR while the third achieved a partial remission (PR). Similar to the clinical outcomes at the NCI, 1 of these patients experienced a prolonged (>6 months) B-cell aplasia. The authors recently reported the largest cohort of CLL patients treated with CD19-targeted T cells (**Fig. 1**).[2] Outcomes in these patients included objective responses with lymph node reductions and B-cell aplasia.[2] Furthermore, this trial included a unique secondary end point evaluating the requirement for conditioning therapy before gene-modified T-cell infusion. Lastly, investigators at the Baylor College of Medicine reported the results of 6 patients with B-cell malignancies, 1 of whom had CLL.[7] Although no objective response was detected, the patient did have stable disease (SD) for 10 months after T-cell infusion. Of note, this trial did not include prior conditioning chemotherapy.

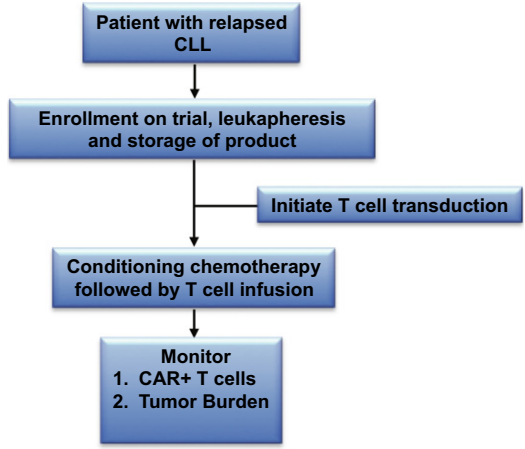

Fig. 1. Memorial Sloan-Kettering Cancer Center (MSKCC) treatment schema using CAR-modified T cells for patients with relapsed CLL. Patients with relapsed CLL are eligible for enrollment, leukapheresis, and infusion with CAR-modified T cells after treatment with conditioning chemotherapy.