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Advances in T-cell therapy for ALL

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CD19-directed chimeric antigen receptor T cells (CART19 or CTL019) have been used with success in pediatric and adult acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL) patients. While this therapy has caused toxicities, including cytokine release syndrome and macrophage activation syndrome, these conditions are reversible with IL-6 blockade using the monoclonal antibody tocilizumab. Furthermore, 90% of the very high-risk patients who underwent infusion with CTL019 achieved a complete response, despite the fact that they previously failed multiple therapies and/or transplant. With improved cell persistence, this immunotherapy may one day prove to be more than a bridge to transplant and may in fact be a transplant alternative.

Introduction

Outcome for patients in second or later relapse of acute lymphocytic leukemia (ALL) is dismal. It is common to draw the conclusion that ALL is a solved problem in pediatric oncology because 85% or more of pediatric ALL patients do very well. However, leukemia is still the most common cause of pediatric cancer mortality, and adult patients do not achieve the cure rates that pediatric patients do. Furthermore, as outcomes have improved with initial treatment, results for those who do not respond to first-line treatment are getting worse. Patients who relapse are harder to get back into remission, harder to get to transplant, and much harder to cure. Consequently, novel therapies are absolutely still needed in ALL for adults and for those pediatric patients who relapse. In the future, as genomic

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characterization of ALL and identification of high-risk genetic lesions becomes and established part of clinical practice, these patients may also be candidates for advanced therapies.

There are a variety of roadblocks to successful cellular immunotherapy for cancer (Table 1). First is the need to target the T cells to recognize and attack the cancer cell. The notion of engineering T cells to attack cancer has existed for over 20 years, with Eschar suggesting the "T body" approach of an artificial T cell receptor [1,2] that has evolved into the chimeric antigen receptor (CAR) of today [3,4]. However, it has taken time and work by many groups before these ideas could be translated into dramatic responses against CD19-positive leukemia and lymphoma.

The second problem is the ability to expand cells ex vivo at the appropriate number for clinical use. Engineered cells can be grown to large numbers under good manufacturing practice (GMP) conditions compatible with clinical use. However, the key is what happens after they are infused into the patient: for optimal clinical responses, engineered cells have to be able to proliferate in an antigen-driven fashion, expand significantly, and ideally persist, providing long-term immunosurveillance. This has not happened in many of the clinical trials testing gene-modified T cells. Ideally, these T cells will provide a key function of normal T cells: persist and seek antigen, which constitutes immunological memory. Excitingly, a number of groups are now getting a handle on what is required for successful cellular immunotherapy for cancer, with improvements evident in each of these key areas [5–9].

Chimeric antigen receptor (CAR) modified T cells

One strategy is to genetically modify T cells to express an antigen recognition domain of a specific antibody, such as one recognizing the B cell antigen CD19, allowing T cells to seek out a CD19-positive tumor. But CD19-positive diseases do not all respond alike. For example, chronic lymphocytic leukemia is different from ALL, which may or may not be different from some non-Hodgkin's lymphomas. The targeting portion of a CAR molecule is generally a single chain variable fragment (scFv). In principle, an scFv can be made from any monoclonal antibody with a desired specificity, and from this scFv sequence a CAR with identical specificity can be created. However CARs cannot differentiate between a normal cell that expressed the targeted antigen and a cancerous cell. In the case of CD19, the normal cell targeted is a B cell, and B cell aplasia is treatable with intravenous immunoglobulin infusions. In other diseases, depending on the antigen targeted, the risk of on-target, off-tissue toxicity can be a major concern [10], which is particularly the case for some solid tumor-associated antigens.

While the scFv provides antigen specificity, CAR-modified T cells must then be activated with an activation domain. CD3 zeta has been used to provide the T-cell activation signal (signal 1). A recent innovation that has greatly increased the success of this approach is the addition of a costimulatory signal (signal 2) to the CAR design. A number of groups have focused on the CD28 [5,6,9] costimulatory domain, and our group at the University of Pennsylvania focused on 4-1BB (CD137) [7,8,11,12]. The use of a CD3 zeta domain only has been referred to as a first generation CAR, and the addition of a single (second generation) or multiple costimulatory domains (third generation) is seen in almost all current CAR designs [13]. CARs in clinical use in which high-level proliferation and high percentages of clinical responses have been reported are all currently second generation.

To activate and expand the genetically modified T cells, some combination of these signals must also be provided during the culture process. Many prior trials utilized an approach of OKT3 (which binds CD3) and IL-2 to activate and expand the T cells [14,15]. More recently, several groups have utilized a

Table 1
Roadblocks to successful cellular immunotherapy for cancer.

Problem	Solution
Targeting	CAR or TCR
Expansion ex vivo	GMP cell culture
Expansion in the host	?Young T cells
Persistence	?Memory T cells

CAR, chimeric antigen receptor; GMP, good manufacturing practice; TCR, T-cell receptor.