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Improving therapy of chronic lymphocytic leukemia with chimeric antigen receptor T cells

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ABSTRACT

Adoptive cell immunotherapy for the treatment of chronic lymphocytic leukemia (CLL) has heralded a new era of synthetic biology. The infusion of genetically engineered, autologous chimeric antigen receptor (CAR) T cells directed against CD19 expressed by normal and malignant B cells represents a novel approach to cancer therapy. The results of recent clinical trials of CAR T cells in relapsed and refractory CLL have demonstrated long-term disease-free remissions, underscoring the power of harnessing and redirecting the immune system against cancer. This review will briefly summarize T-cell therapies in development for CLL disease. We discuss the role of T-cell function and phenotype, T-cell culture optimization, CAR design, and approaches to potentiate the survival and anti-tumor effects of infused lymphocytes. Future efforts will focus on improving the efficacy of CAR T cells for the treatment of CLL and incorporating adoptive cell immunotherapy into standard medical management of CLL.

1. Overview of chronic lymphocytic leukemia

1.1. The current rules of the road for cellular therapies

Chronic lymphocytic leukemia (CLL) is a malignant disease of mature B cells, but the clinical course is variable; some patients never require treatment, and others have a rapidly progressive and fatal course. Accordingly, current guidelines suggest that therapy should be reserved for patients with symptomatic or progressive disease. The vast majority of CLL patients will at some point develop symptomatic disease requiring therapy. With the exception of cellular therapy with allogeneic stem cell transplantation (SCT), CLL remains incurable with standard treatment options. However, the advanced age of individuals and comorbidities at the time of CLL diagnosis (or need for treatment) can pose a barrier to transplant options. SCT carries significant risks of treatment-related mortality, due to toxicities of the conditioning regimen, graft-versus-host disease (GvHD), and immunosuppression. Many patients are unable to tolerate either the conditioning regimen or the medications used to prevent or treat GvHD. In addition, identifying suitably matched donors can be challenging, particularly in non-Caucasian populations. At best, sustained remission of high-risk CLL disease is observed in up to 50% of allogeneic transplant recipients [1]. Finally, the optimal timing of pursuing transplant options is a matter of discussion and research [2] particularly because novel agents show significant therapeutic benefits.

Recently described targeted therapies that inhibit B-cell signaling pathways such as ibrutinib (an inhibitor of Bruton agammaglobulinemia tyrosine kinase) [3] and idelalisib (PI3 kinase p110δ inhibitor) [4] have demonstrated remarkable activity in CLL. Both ibrutinib and idelalisib (in combination with rituximab) were approved for the treatment of CLL patients who have failed at least one prior therapy, or in first-line when *TP53* is absent or mutated and fludarabine-based therapy is not effective [5]. Even though these therapies effect robust responses in high-risk CLL, they are administered continuously and have not yet demonstrated the ability to induce cures [6,7].

Patients with CLL who do go on to allogeneic hematopoietic stem cell transplant (HSCT) may achieve long-term durable remissions; these are almost always associated with some degree of chronic GvHD [8]. Relapse can sometimes be treated with donor lymphocyte infusion, which can re-induce remission [9]. These two findings suggest that T cells are the active agents in effecting long-term remission or even a potential cure of CLL. However, unmodified autologous T lymphocytes are unlikely to recognize or respond to CLL tumor cells due to immunological tolerance. Genetic manipulation and infusion of autologous T-cell–based therapies is a way of breaking tolerance and has the tantalizing

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