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Chimeric antigen receptor T cell therapy in AML: How close are we?

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The majority of patients presenting with acute myeloid leukemia (AML) initially respond to chemotherapy but post-remission therapy is required to consolidate this response and achieve long-term disease-free survival. The most effective form of post-remission therapy relies on T cell immunotherapy in the form of allogeneic hematopoietic cell transplantation (HCT). However, patients with active disease cannot usually expect to be cured with HCT. This inherent dichotomy implies that traditional T cell-based immunotherapy in the form of allogeneic HCT stops being efficacious somewhere between the measurable residual disease (MRD) and the morphologically obvious range. This is in part because the full power of T cells must be restrained in order to avoid lethal graft-versus-host disease (GVHD) and partly because only a subpopulation of donor T cells are expected to be able to recognize AML cells via their T cell receptor. Chimeric antigen receptor (CAR) T cell therapy, most advanced in the treatment of patients with B-cell malignancies, may circumvent some of these limitations. However, major challenges remain to be overcome before CAR T cell therapy can be safely applied to AML.

Introduction

Immunotherapy has revolutionized the treatment of a variety of advanced malignancies. Complete remissions have been reported in over 90% of patients with relapsed B-cell acute lymphoblastic

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leukemia (B-ALL) who receive anti-CD19 chimeric antigen receptor redirected T cells (CTL019 or CART-19) [1–3]. How to translate the success of CART cell therapy to other malignancies with unmet medical need such as acute myeloid leukemia (AML) remains an important question in the field.

CART cells recognize their target antigen via an interaction between the chimeric immunoreceptor and a cell surface ligand. The success of CART-19 is predicated on two factors: (1) massive expansion and persistence of the infused T cells, and (2) tolerability of CD19+ (B-cell) aplasia. The most common side effect of CART-19 is depletion of endogenous normal B-cells, yet protracted B-cell aplasia is well tolerated by patients [4,5]. Thus, a critical requirement of CART cell therapy is that the target tissue be expendable. AML is a malignancy of the hematopoietic stem/progenitor cells (HSPC) and shares cell surface antigens with normal HSPC and with normal myeloid progeny such as neutrophils and monocytes [6,7]. Hence, there is no truly AML-specific surface molecule. Several groups have demonstrated in mouse xenografts that anti-CD33 or anti-CD123 CAR T cells (CART-33 or CART-123) can eradicate AML but also lead to profound myeloablation [8–11]. Thus, although the efficacy of anti-AML CAR T cells appears equivalent to that of anti-ALL CAR T cells, hematopoietic toxicity is likely to be unacceptable. Here, I will review the absolute requirements for successful CAR T cell therapy of AML (potency, target specificity, cell surface antigen expression, and persistence), describe what progress has been made in the field, and outline what challenges remain.

Potency

CAR T cell-based therapeutics are likely more potent than equivalent monoclonal antibodies with which they share a targeting domain (single chain variable fragment). In fact, it is likely that CAR T cells are more potent than the equivalent bi-specific T cell engagers as well [1,8,12–14]. Thus, clinical outcomes and toxicities observed on therapeutic trials of monoclonal antibodies or antibody-drug conjugates (ADC) cannot be extrapolated to CAR T cells. In AML there is extensive clinical experience with the anti-CD33 ADC gemtuzumab ozogamicin (GO) and experience is accruing with “naked” as well as conjugated CD123-specific compounds. Overall, responses to these agents as monotherapy are very limited [15–17] and toxicity is not prohibitive. In contrast, single administration of anti-CD33 or anti-CD123 CAR T cells leads to eradication of AML in xenograft mouse models along with irreversible marrow aplasia, related to expression of these antigens on normal marrow progenitors [9]. Thus, it would seem that potency against malignant myeloid cells correlates with toxicity against normal myeloid cells.

Target specificity to hematopoietic tissue

Hematopoietic toxicity is manageable with good supportive care, particularly if transient. However, transgenic T cells can traffic to non-hematopoietic organs and have been found throughout the body at autopsy of patients dying from on-target specificity against non-hematopoietic tissues [18–20]. Thus, it is critical that putative targets of anti-AML CAR T cells be restricted to hematopoietic tissues. In this context, Table 1 lists some of the cell surface targets in AML that have been evaluated or are under evaluation for CAR or antibody-based therapeutics along with their potential for off-target toxicity.

Cell surface antigen target

Since CAR T cells rely on antibody-like recognition, only cell surface antigens are suitable for targeting. While the advantage is non MHC-restricted recognition and the lack of requirement for antigen presentation, the disadvantage is that most tumor-specific antigens are intracellular and thus not accessible to CAR T cells. One potential way to target intracellular antigens is using novel constructs that are based on antibodies recognizing peptide/MHC complexes [21]. While this approach paves the way to targeting leukemia-associated antigens (LAA) such as WT1 or PR3 and even leukemia-specific mutations (if the relevant peptides are presented on MHC, which is not a given), it is significantly limited by the same issues that bedevil T cell receptor (TCR)-based therapeutics, namely HLA restriction (each antibody will only recognize peptide in the context of a specific HLA molecule) and HLA dependency (downregulation of HLA molecules is a classic tumor escape mechanism), as well as the sheer