CAR Therapy—the CD19 Paradigm

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One of the major limitations of most existing cancer therapeutics is the lack of specificity or curative potential. The goals of T cell immunotherapy are to achieve curative potential through the combination of potency, specificity, and persistency of therapeutic effect (Table 1). The genetic engineering of T cells provides a means to rapidly generate antitumor T cells for any cancer patient. This approach is predicated on gene transfer technology that enables the expression of receptors for antigen and other gene products in patient T cells. Indeed, T cells can be genetically targeted to any antigen and enhanced to overcome immune-escape mechanisms to achieve tumor eradication.

Chimeric antigen receptors (CARs) are synthetic receptors that, in a single molecule, redirect T cell specificity and enhance antitumor potency. Functional augmentation is achieved through the design of “second-generation CARs” that reprogram T cell function through their costimulatory properties. The combined costimulatory domains incorporated in second-generation CARs critically determine the function, differentiation, metabolism, and persistence of engineered T cells. Two decades ago, CD19 emerged as the prime target for developing our CAR technology and provided the first proof-of-principle that CD19-targeted human peripheral blood T cells could eradicate a broad range of B cell malignancies in immunodeficient mice. CD19 has since become the model for CAR therapies. CD19 CARs that incorporate either CD28 or 4-1BB signaling domains are the best known to date, and both have yielded dramatic outcomes in pediatric and adult patients.

Several phase I trials have demonstrated high rates of complete response (CR) to CD19 CAR therapy in patients with non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and, most dramatically, acute lymphoblastic leukemia (ALL). At the 2015 American Society of Clinical Oncology (ASCO) annual meeting, researchers from Memorial Sloan Kettering Cancer Center in New York presented updated findings from a phase 1 trial of CD19 CAR therapy in patients with relapsed or refractory B-cell ALL. To date, the trial has enrolled 39 patients (median age, 45 years), including 13 patients (33%) with Philadelphia chromosome (Ph)-positive ALL and 4 patients (11%) with the T315I mutation. The CR rate was 87%, which was achieved by a median of 23 days. Furthermore, of 32 evaluable patients with minimal residual disease (MRD) at baseline, the MRD-negative CR rate was 81%. A subgroup analysis showed consistently high CR rates and MRD-negative CR rates across patient subgroups defined by baseline disease burden, prior allogeneic hematopoietic stem cell transplant (allo-HSCT), prior lines of therapy, age, and Ph-positive status.

Cytokine release syndrome (CRS) is the most common and potentially severe toxicity associated with CAR T cell therapy. CRS appears to be an inflammatory process associated with an intense antitumor response mediated by exponential T-cell proliferation. Severe CRS can induce hemodynamic and cardiac side effects, including shock and multisystem organ failure. Patients who develop severe CRS may require treatment with corticosteroids, IL-6 receptor blockade (e.g., tocilizumab), vasopressors, and/or supportive therapy. Several research groups have proposed case definitions of CRS, with the goal of identifying patients at a high risk for toxicity. High disease burden at infusion and elevated C-reactive protein (CRP) levels have emerged as potential predictors of severe CRS. On June 10, 2015, the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) held a special workshop on CRS after T-cell immunotherapy to better understand this toxicity and its management.

Building on the success of CAR therapy in hematologic malignancies, recent research has focused on the possibility of similar therapeutic approaches for patients with solid tumors. Mesothelin is a cell-surface antigen that is selectively expressed in mesothelioma and a range of other solid tumors, including ovarian, breast, and pancreatic cancers. Although inefficient T cell tumor infiltration is a potential obstacle to solid tumor therapy, researchers recently demonstrated the feasibility and efficacy of regional T cell delivery. In
2 Cancer Vaccines and Immunomodulatory Therapy

Table 1. Goals of T-Cell Engineering in Oncology

- Overcome central immune tolerance
- Circumvent human leukocyte antigen (HLA) downregulation
- Target both CD4+ and CD8+ T cells to the tumor
- Broaden T-cell reactivity
- Target cancer stem cells
- Enhance T-cell potency
- Modulate T-cell longevity
- Exploit alternative (nonautologous) T-cell resources

an animal model of human pleural malignancy, intrapleural T cell administration substantially outperformed systemically infused T cells, requiring 30-fold fewer T cells to induce long-term complete remissions. Researchers at the Memorial Sloan Kettering Cancer Center in New York are conducting a phase I trial of mesothelin-targeted T cells administered intrapleurally as a single infusion in patients with malignant pleural disease due to mesothelioma, lung cancer, or breast cancer (NCT02414269). Other research groups are also evaluating mesothelin-directed CAR T-cell therapy in patients with solid tumors (NCT01583686, NCT02159716, NCT02465983).

Summary

CD19-targeted CARs provide new options for cancer treatment by inducing complete responses where standard chemotherapeutic agents have failed. Future directions in CAR therapy include novel methods of target-cell identification, including combination antigen recognition and target discovery (i.e., proteomics); options for increased potency through the use of combination regimens, optimized T cell delivery, and graded costimulatory support; and the identification of alternative T cell sources. With ongoing studies in hematologic malignancies as well as solid tumors, CAR T cell therapy promises to play an increasing role in cancer treatment.

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