Perspective

CAR T Cells: A Look Under the Hood and Down the Road

Mark J. Adler, MD

DISCLOSURES | September 16, 2014

Use of CARs to treat solid tumors presents daunting challenges not present in hematologic malignancies. The size alone of solid tumor masses, typically millions to billions of times larger than separate single, floating cells, has long been a barrier to immune strategies. T-cell immunity, often metaphorically described as "soldier" cells engaged in cell-to-cell combat, would, in the case of CARs and solid tumors, be the equivalent of sending foot soldiers to destroy a massive fortress. Within such a mass, moreover, local factors would include impaired vascular access and a different milieu within areas of central tumor necrosis. Even if CARs could find their way inside these masses, differences in such metabolic parameters as local pH and O_2 content could vastly alter antigen affinity. Altered biochemical mechanisms ranging from cytokine release and action to cellular and protein interactions could neutralize CAR effectiveness. Assuming that these towering obstacles could be overcome, the CAR methodology might find a useful adjunctive role of "cleaning up" residual disease after surgical or chemical debulking.

The lack of constancy, homogeneity, and uniformity of cells and targets has been the bane of oncologic approaches in solid tumors. We have seen dramatic responses, frequently complete remissions—even in that most lethal beast, small cell lung cancer; unfortunately, even after complete remissions, chemoresistant cells pop up, multiply, and rapidly overpower the patient. We see hormone-resistant tumors emerge after early success with hormonal therapy for breast and prostate cancers. Even with hematologic malignancies, which appear to uniformly express CD19, we have seen relapse following the emergence of CD19-negative leukemic cell populations after CAR T-cell therapy.[13,14] Cancer is a dynamic and feisty opponent.

CARs and TRUCKs

The recognition of cancer cell variants that do not express the desired target has led to an exciting strategy utilizing so called TRUCKs (T cells Redirected for Universal Cytokine Killing). To construct TRUCKs, CAR T cells are engineered with the additional capacity to induce IL-12 production; activation of CARs by specific antigen recognition causes release of IL-12 which, in turn, attracts immune cells, including natural killer cells and macrophages, to attack tumor cells. Heterogeneous tumor cells in the vicinity, which lacked the antigen and were therefore invisible to CAR recognition, can now be destroyed.[11] Preclinical data are encouraging and clinical trials using TRUCKs have commenced.

Toxicities observed with CAR T cells might be considered relatively modest compared with classic cytotoxic agents and sometimes with targeted biological small drugs such as the tyrosine kinases. However, the toxicities associated with immune storms or cytokine release syndromes are not trivial and indeed may be life-threatening. One of the perennial challenges in trying to ameliorate side effects and symptoms of all immune-based therapy

remains: identification and separation of mechanisms responsible for unnecessary toxicity from those that are crucial for the intended therapeutic effect.

Beyond the expected risks of exaggerated, generalized immune reactions, severe damage has been attributable in some instances to attack upon the right antigen in the wrong place. In one of the few solid tumor studies using CAR T cells, CARs targeting HER2/*neu* were used to treat a patient with antigen-expressing metastatic colon cancer.[15] Rapidly following infusion of the CAR T cells, the patient experienced progressive and severe respiratory distress and died within 5 days despite intensive medical care. Evaluation of circulating cytokines suggested a cytokine storm, which researchers speculated to be triggered by the presence of antigen on pulmonary epithelial cells. This effect was analogous in some respects to the well-recognized cardiac toxicity of trastuzumab when its use against breast cancer leads to inadvertent binding to HER2 antigen on cardiac muscle.

The Road Ahead

Overall, CAR T cells represent advancement toward therapy with greater specificity and efficacy and less toxicity. The processes required to generate CARs remain logistically complex, individualized, confined to a narrow tumor spectrum, and expensive. However, efforts are under way to eliminate the need for patient-specific T cells, with the ultimate goal of developing universal, off-the-shelf T-cell products.[16]

Just as major advances against solid tumors (including testicular and ovarian cancers) came with the advent of combination chemotherapy, so too may we anticipate combined immunologic approaches. Already, different tyrosine

kinase inhibitors are being combined, and preclinical work has shown evidence of increased therapeutic effect when CAR T cells are given in conjunction with antibody to PD-1.[17]

The current surge of novel immune-based therapies, particularly the engineering feats of CARs and TRUCKs, have raised hopes for cancer immunotherapies, but researchers and clinicians have many miles to go on the road ahead.

References

Cite this article: Mark J. Adler. CAR T Cells: A Look Under the Hood and Down the Road - Medscape - Sep 16, 2014.