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Are Chimeric Antigen Receptor T Cells Ready for Prime Time?

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H&O Could you please give a brief review of how chimeric antigen receptor (CAR) T cells work?

RB Many tumors do not express antigens that the immune system recognizes as foreign, so the immune system never gets activated. In other cases, the immune system does recognize the tumor initially, but the tumor suppresses the immune response. The goal of CAR T-cell treatment is to genetically engineer the immune system to overcome these obstacles, and to recognize tumor cells that it otherwise would not recognize.

CARs are part antibody and part T-cell receptor. We retrieve a patient's T cells and use retroviral or lentiviral vectors in the lab to insert genes that recognize proteins on the surface of tumor cells. These modified cells now have their own specificity through their native T-cell receptor, and all of them can recognize the target antigen through the CAR that they were designed to recognize. They are infused into the body, where they work equally well in CD4 and CD8 cells.

H&O What makes CAR T cells such an attractive area for study?

RB First, they give us the ability to generate CAR T cells that can target virtually any antigen on the surface of a tumor cell. Second, we are using the patient's own immune system to combat his or her tumors. Finally, the engineered cells can be made relatively quickly.

H&O In what types of cancer have they been studied so far?

RB They have been studied in multiple cancers, but not with universally effective antitumor effects. The initial study of 3 patients that was published by Carl June's group at the University of Pennsylvania looked at chronic lymphocytic leukemia (CLL), with promising results.

The most prominent clinical outcomes have been related to targeting CD19 in B-cell acute lymphoblastic leukemia (ALL). We at Memorial Sloan Kettering Cancer Center were the first group to publish results in ALL. We conducted the procedure in 5 adults with relapsed ALL and achieved complete remission in all 5; we published our results in *Science Translational Medicine* in 2013 and received a great deal of press attention. Several weeks later, researchers including Stephen Grupp at the Children's Hospital of Philadelphia published results of CD19-targeted CAR T-cell therapy in the *New England Journal of Medicine* in 2 children with ALL. Researchers at the National Cancer Institute in Rockville, Maryland, and the Fred Hutchinson Cancer Center in Seattle, Washington, also have

investigated the use of CAR T cells in B-cell ALL. We have seen a complete response rate across all centers of 80% to 90% in both adult and pediatric patients, which is very encouraging, and we are continuing to conduct trials of CAR T cells in B-cell ALL (NCT01044069 and NCT02535364).

H&O What is the duration of response in these patients?

RB Although it is too early to know, we do have some data on patients who had the treatment 1, 2, or 3 years ago. We have seen relapses in some of these patients, and sometimes the relapsed disease lacks expression of CD19. That is to say, the tumor has found an additional way to escape detection by the immune system—or in this case, by the CD19-targeted CAR T cells.

H&O What results have been seen in patients with other types of disease?

RB We have seen significant but somewhat less impressive results with CAR T cells in diffuse large B-cell lymphomas and in low-grade B-cell cancers, such as CLL and follicular lymphoma.

Most of the success with this technology has been seen in the context of blood tumors. Applying this technology to solid tumors may be more difficult because solid tumors may create a more suppressive tumor microenvironment. In addition, target antigen expression is probably more heterogeneous in solid tumors than in liquid tumors.

Do the results we have seen so far simply mean that we have an improved therapy for patients with relapsed B-cell ALL? Or do they have further implications, as proof of principle for an approach that might be used in any type of cancer in which a suitable target antigen can be identified? I favor the second option, bearing in mind that not all of the tumor cells are likely to express the target antigen. A potential way to overcome this limitation is to recruit the endogenous immune system with immune checkpoint blockade; another is to target more than 1 antigen on the tumor cell surface.

H&O What are the risks of CAR T-cell treatment?

RB The first risk is that the antigen being targeted on the tumor also is expressed by normal, healthy tissue. We call that an *on-target, off-tumor effect*. Unfortunately, all the mouse studies in the world do not negate the possibility of this occurring in the clinical setting, which is why it is important to start treatment with a very low dose of CAR T cells. Investigators should also maintain control over CAR T cells, either through the introduction of suicide genes or through temporary expression of the chimeric receptor by the T cell.

The second risk is that the T cells will have a stronger immune response to the tumor than anticipated, causing a cytokine release syndrome. This syndrome leads to a high fever and can cause a drop in blood pressure, or even neurologic changes in the case of CD19-specific CAR T cells. We did not see this reaction in our preclinical mouse models, but we have seen it in patients in all of our study centers.

Fortunately, both of these scenarios can be clinically managed and are fully reversible.

H&O Is cytokine release syndrome a sign that the treatment is working well?

RB Cytokine release syndrome shows that a significant immune response against the tumor is being mediated by the infused CAR T cells. It correlates with the amount of tumor patients have; patients with a lower tumor burden are less likely to develop that side effect. Having said that, there are patients who never have cytokine release syndrome but who do just as well clinically as those who do.

H&O How has CAR T-cell treatment evolved since it was first introduced?

RB We have passed several milestones. When we first started working on this CAR T-cell approach approximately 2 decades ago, the receptor had a simpler design. We later realized that making the receptor more complex, as we have done with second- and third-generation CARs, would increase its potency and make it signal better in the T cells. We have also seen, based on work performed at the National Cancer Institute, that conditioning chemotherapy should be given prior to infusion of the CAR T cells. We do not understand the mechanism by which this works, but it is clear that administering chemotherapy several days before CAR T cells appears to enhance antitumor activity.

H&O How have CAR T-cell targets evolved?

RB CD19 remains the most prominent antigen target in CAR T-cell therapy, but a large number of other targets for B-cell cancers are being explored, including CD20. A newer target is CD22, which is of special interest because it is expressed in the tumor cells of some patients with ALL who have relapsed disease after CD19 CAR T-cell therapy. Several groups, including ours, are investigating a solid tumor antigen called mesothelin, which is expressed in mesothelioma, lung cancer, breast cancer, and pancreatic cancer. Our group is also investigating MUC16, which is overexpressed in ovarian cancers (NCT02498912). We are also targeting prostate-specific membrane antigen (PSMA) for the treatment of metastatic prostate cancer (NCT01140373). There are many additional targets being studied as this phase of therapy moves beyond B-cell cancers.

H&O Could you talk more about your own work with CAR T cells at Memorial Sloan Kettering?

RB We are developing what we call “armored” CAR T cells in our lab and in the lab of Dr Michel Sadelain. With armored CAR T cells, not only do we modify the T cells to express the chimeric receptor, we also engineer them to express biologically active immune modulators. For example, modifying a CAR T cell to express the proinflammatory cytokine interleukin 12 has the potential to protect the cell from inhibition within the tumor microenvironment. We can also modify CAR T cells to express the costimulatory ligands 4-1BB and CD40L. We are investigating the use of armored CAR T cells in next-generation trials for CLL (NCT01416974 and NCT00466531), and as I mentioned earlier, we are embarking on an ovarian cancer trial in which we are coupling interleukin 12 secretion with MUC16-targeted CAR T cells.

Armored CARs are exciting because they address some of the limitations of this technology in its first iteration. We are also hoping to control toxicity with the additional modification of T cells with various elimination and suicide genes.

Dr Jae Park gave an oral presentation at the American Society of Hematology annual meeting on one of our ALL studies at Memorial Sloan Kettering, and Dr Kevin Curran presented a poster with our B-cell pediatric data.

H&O Do you think that making prepackaged CAR T cells is a viable alternative to working with autologous T cells?

RB The goals of speeding up the process and bringing down the cost are worthy ones, but researchers may be spending a lot of time trying to fix a problem that will solve itself. That is, I believe that the cost of autologous CAR T-cell engineering will automatically come down on its own. At least for now, I would prefer to focus on improving CAR T-cell technology with freshly modified T cells, rather than trying to turn it into an off-the-shelf product.

H&O How close is industry to being able to submit CAR T cells to the US Food and Drug Administration (FDA)?

RB Several companies are already running phase 2 registration trials, so I do not think it would be unreasonable to see the FDA giving initial approval to CAR T-cell therapy in selected malignancies within the next few years.

Suggested Readings

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