Chimeric Antigen Receptor T-Cell Therapy Targeting CD30 in Hodgkin Lymphoma

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H&O What prompted your research of chimeric antigen receptor (CAR) T-cell therapy in Hodgkin lymphoma?

BS It has been known for a long time that Hodgkin lymphoma is susceptible to T-cell immune-mediated treatment. As researchers at Baylor College of Medicine, my colleagues and I evaluated the possibility of using T cells to target the Epstein-Barr virus, which is expressed in approximately 40% of patients with Hodgkin lymphoma. We found that targeting antigens associated with this virus with specific T cells can reduce disease progression and thereby induce complete remissions, which can be sustained in a good number of patients. A drawback to this approach is that only a small subset of patients is eligible for treatment.

When looking for an alternative, we focused on CD30, which is expressed by all malignant Reed–Sternberg cells in Hodgkin lymphoma. At the time, there was evidence that brentuximab vedotin (Adcetris, Seagen), an antibody-based immunotherapy, successfully targeted this molecule. Like all antibodies, brentuximab vedotin has some transient effects. Brentuximab vedotin is also associated with some neuropathy. We aimed to leverage the success of CAR T-cell therapy, combining the CD30 antibody–based specificity with the potent cytotoxic activity of T cells. By targeting CD30, treatment would be broadly applicable to all patients with Hodgkin lymphoma. It also offers the opportunity to overcome some of the other strategies that this tumor employs to bypass immune recognition because CAR T cells do not require an intact antigen-presentation machinery for tumor targeting.

H&O What did your pilot study from 2017 show?

BS This phase 1, dose-escalation trial was the first-in-human study of this specific chimeric antigen receptor targeting the CD30 antigen, known as CD30.CAR. The study opened in 2011, approximately at the same time that the early CAR T-cell trials targeting CD19 were being conducted. Therefore, there was limited experience with this type of treatment. Because it was a first-in-human study, we did not administer lymphodepletion therapy prior to the CD30.CAR T-cell infusion. The dose escalation involved increasing the number of cells that were infused into patients. In the study, we treated 9 patients with CD30-positive disease: 6 had Hodgkin lymphoma, 2 had anaplastic large-cell lymphoma, and 1 had a composite lymphoma (diffuse large B-cell lymphoma evolved to Hodgkin lymphoma).

The study showed that the treatment was safe. In addition, the CAR T cells were able to expand within the patients postinfusion. There was some promising antitumor activity in the 3 patients who achieved a complete remission and in 3 others who achieved stable disease. This study was the first to show the direct effects of the CAR, and these results were achieved without lymphodepletion, which is now known to further improve outcome.

H&O Could you please describe your more recent phase 1/2 study of the anti-CD30 CAR T-cell therapy?

BS This phase 1/2 study encompasses the second part of the journey. The study was conducted at the University of North Carolina and Baylor College of Medicine, where I was trained. Researchers at these institutions have been collaborating for some time. The study was conducted in parallel, using the same protocol for the expansion and manufacturing of the CAR T cells. Treatment began with lymphodepletion, which provides an ideal milieu in which the CAR T cells can proliferate. The lymphodepletion regimen differed between the 2 institutions. Fludarabine was used in combination with either bendamustine or cyclophosphamide. Cyclophosphamide is one of the most frequently used agents for lymphodepletion for CAR T-cell therapies. Bendamustine was included as an alternative lymphodepletion agent, and was equally effective. The primary endpoint of the study was safety.

We treated 41 patients in the study. Among these patients, 37 had measurable disease at the time the CAR T cells were infused. The overall response rate was 62%, with a complete response rate of 51%. This response was sustained over time.

H&O Were the adverse events similar to those seen with CAR T-cell therapy in other settings?

BS The study showed much lower toxicity, which was welcome. Cytokine release syndrome is often observed after CAR T-cell infusion, especially when targeting the CD19 antigen in leukemia and lymphoma. In our study, cytokine release syndrome was less frequent (24%), and those few cases were very mild. Neurotoxicity is another serious complication often associated with CAR T-cell therapy targeting CD19. In our study, no patients experienced neurotoxicity. A proportion of patients in our study experienced some prolonged cytopenia, which is a common event that can be attributed to lymphodepletion. It was not surprising to see cytopenia because these patients were heavily pretreated. Their hematopoietic reserves were probably not normal.

An unexpected finding was a mild, transient skin rash. The pathogenesis was unknown. The rash did not require any treatment to resolve.

H&O Were there any surprising findings from the study?

BS The minimal toxicity could be considered surprising because neurotoxicity and serious cases of cytokine release syndrome are common in other trials of CAR T-cell therapy. The CAR T-cell treatment in this study was very effective, with minimal toxicity. The response rate in this particular patient population was remarkable. These patients had progressed during treatment with the standard of care and multiple lines of therapy. Most patients had also progressed during treatment with novel immunotherapies, such as brentuximab vedotin or checkpoint inhibitors.

We aimed to leverage the success of CAR T-cell therapy, combining the CD30 antibody–based specificity with the cytotoxic activity of T cells.

H&O Which types of patients are better candidates for this treatment?

BS Older and/or frail patients would benefit from the low toxicity of this treatment. Hodgkin lymphoma often affects older patients. There are chemotherapy regimens that can produce and promote responses, but older patients may have comorbidities and may be more susceptible to the side effects of these therapies.

Younger patients are also candidates, however. In Hodgkin lymphoma, there are multi-line therapies that can produce responses, but these treatments are associated with substantial toxicity. Administering a treatment earlier in the disease course will most likely minimize or limit the morbidity and long-term sequelae seen in younger patients with Hodgkin lymphoma. Good candidates would also be patients at risk of toxicity from other immunotherapies, such as the severe neuropathy that some patients experience with brentuximab vedotin.

H&O What are some areas of future research?

BS Now that we have this treatment, researchers should further evaluate the effect of CAR T cells in the tumor microenvironment of patients with Hodgkin lymphoma. This disease is associated with a complex and highly inhibitory tumor microenvironment. Data showing efficacy of

CAR T cells in this setting can represent a model to study the challenges with this treatment in the solid tumor setting. The success in Hodgkin lymphoma presents an excellent platform from which to test the next generation of CAR T-cell therapy.

H&O What is next for CAR T-cell therapy in Hodgkin lymphoma?

BS There are 2 important aspects to consider while we explore the use of CAR T-cell therapy in this setting. First, there is the potential to combine CAR T-cell therapy with other agents. In Hodgkin lymphoma, checkpoint inhibitors are a promising treatment because they synergize with T cells. The combination of CAR T-cell therapy and checkpoint inhibitors is promising, especially in a disease such as Hodgkin lymphoma, where both treatments have shown efficacy. In our trials, some of the patients who relapsed after treatment with CAR T cells went on to receive a checkpoint inhibitor and responded to this therapy, although they had not before. There is a possibility that CAR T-cell therapy can spark immune cell death within the tumor microenvironment that induces further mechanisms of tumor recognition, a phenomenon known as cross-presentation or antigen epitope spreading. This possibility further strengthens the rationale for combining these treatments.

Another aspect to explore is how to improve trafficking of CAR T cells to the tumor. Hodgkin lymphoma is not a circulating tumor, but rather it is localized to areas where T-cell trafficking may not be ideal. Tumors of patients with Hodgkin lymphoma produce chemokines that attract inhibitory cells. The receptor for these chemokines is not expressed on CAR T cells. It should be possible to further engineer T cells to express the appropriate chemokine receptor to improve their homing to the tumors. The goal would be to circumvent the inhibitory mechanism of the tumor microenvironment by bringing more CAR T cells to the tumor.

Disclosure

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Suggested Readings

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