ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

CAR T-Cell Therapy Against B-Cell Maturation Antigen in Multiple Myeloma

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H&O Could you please describe B-cell maturation antigen?

AC B-cell maturation antigen (BCMA) is a cell-surface receptor that is expressed primarily by plasma cells, including malignant plasma cells, which are the primary cancer cells in multiple myeloma. BCMA gained interest as a potential target in multiple myeloma because of its high expression, as well as its role in promoting myeloma cell proliferation and survival. It is expressed in almost every patient with multiple myeloma, although the intensity of expression can vary. BCMA is not expressed by other normal tissues in the body, so it would be expected that a treatment targeting this antigen will have less off-target toxicity.

H&O What was the design of your recent study on the novel CAR T-cell therapy targeting BCMA?

AC This pilot phase 1 study evaluated an autologous chimeric antigen receptor (CAR) T-cell product known as CART-BCMA in patients with relapsed/refractory multiple myeloma. All patients had received at least 3 prior treatments for multiple myeloma, and the median number of prior treatments was 7. The enrollment criteria did not specify a certain level of BCMA expression. BCMA levels were measured as a correlate.

All patients in the study underwent leukapheresis to collect T cells. During the CAR T-cell manufacturing process, patients could receive treatment for multiple myeloma to hold their disease in check. Patients had the engineered T cells infused over 3 days, using a split-dose infusion regimen. Patients received 10% of the dose on the first day. If they did well, they received 30% of the dose on the second day, and then the remaining 60% on the third day. This dosing schedule allowed some flexibility; if patients started to show signs of cytokine release syndrome or other toxicities, the next dose could be held.

We were interested in assessing the impact of lymphodepleting conditioning. The first cohort of patients received the CAR T cells alone, at a dose of 1–5 × 10^8, without any conditioning treatment. The second cohort received conditioning with cyclophosphamide at 1.5 g/m^2 given as a single dose. For safety purposes, the dose of CAR T cells was 1–5 × 10^7, which was tenfold lower than the dose in the first cohort. When this regimen was deemed safe, the third and final cohort of patients received cyclophosphamide conditioning and the full

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dose of CAR T cells: 1–5 × 10^8. The study provided data for the 3 cohorts of patients.

H&O What were the results of the study?

AC Twenty-five patients were treated in the study. Nearly all patients had high-risk cytogenetic features. All patients were heavily pretreated. Almost all were dual refractory to a proteasome inhibitor and an immunomodulatory drug (IMiD). Close to half of patients were penta-refractory, meaning they were refractory to all of the typical agents used for the management of multiple myeloma.

There were responses in all 3 of the cohorts. In the first cohort of patients, who did not receive lymphodepletion therapy, 4 of 9 (44%) had a partial response or better. In the second cohort of patients, who were treated with cyclophosphamide conditioning but a lower dose of CAR T cells, only 1 of 5 (20%) responded. We closed that cohort early. In the third cohort of patients, who were treated with cyclophosphamide and the full dose of CAR T cells, 7 of 11 (63%) had a partial response or better. The study therefore demonstrated that CART-BCMA had activity, even in these heavily pretreated patients.

Most of the responses lasted from 3 to 6 months, and then the disease returned. There were 3 patients with an ongoing response of more than a year, including the first patient treated, who was still in complete remission more than 2 and a half years after treatment.

H&O What were the toxicities?

AC The primary toxicities were similar to those reported in previous studies of CAR T-cell therapies and consisted of cytokine release syndrome and neurotoxicity. Cytokine release syndrome can cause high fevers and flu-like symptoms, with malaise and muscle aches. These symptoms can be severe, leading to low blood pressure and difficulty breathing. In the current study, cytokine release syndrome developed in 22 of the 25 patients (88%). The syndrome was severe in 8 patients (32%). Six patients (24%) required treatment with tocilizumab (Actemra, Genentech), an anti–interleukin 6 receptor agent. The syndrome was reversible in all patients.

Neurotoxicity can cause mild confusion or delirium in the setting of high fever, as well as encephalopathy, which can lead to profound confusion or even coma. In our study, 7 patients developed some degree of neurotoxicity. It was low-grade and transient in 4 patients, and more severe in the other 3. Symptoms were reversible in all patients.

Other adverse events included low blood counts, electrolyte abnormalities, and fatigue. There were no unexpected toxicities or any that were off-target.

H&O What is your overall conclusion from the study, and are there any implications for subsequent clinical trials and/or clinical practice?

AC The study results validate BCMA as a target in multiple myeloma. CART-BCMA was associated with responses in heavily refractory patients with poor-risk features. The toxicity profile of CART-BCMA was similar to that seen with other CAR T-cell therapies, such as those that target CD19. Although there were strong responses in a majority of patients, in most cases, these responses were not durable. An implication for subsequent trials is that enrollment might include patients who have received fewer lines of therapy, whose T cells may be less "beat up" from years of chemotherapy and other treatments. As more patients receive CAR T-cell therapy, for multiple myeloma and other malignancies, physicians are learning how to better manage the associated toxicities. I anticipate that the risk/benefit profile will improve enough to allow treatment of patients earlier in the disease course. At the University of Pennsylvania, we recently opened a clinical trial enrolling patients who have high-risk multiple myeloma, including poor-risk cytogenetic features or primary refractory disease. CAR T-cell therapy will be administered after the first or second line of treatment. The goal is to see if outcomes can be improved by obtaining a durable remission early in the treatment course.

H&O How do data for CART-BCMA compare with data for CAR T-cell therapies in other malignancies?

AC The US Food and Drug Administration (FDA) has approved 2 CAR T-cell therapies, both of which target the CD19 antigen. Axicabtagene ciloleucel (Yescarta, Kite) is approved for adult patients with relapsed/refractory large B-cell lymphoma. Tisagenlecleucel (Kymriah, Novartis) is approved for adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and for children and young adults with B-cell precursor acute lymphoblastic leukemia. The response rates seen with CART-BCMA in multiple myeloma are not quite as high as those seen with other CAR T-cell therapies in acute lymphoblastic leukemia. They are fairly similar to reports in DLBCL and chronic lymphocytic leukemia. One difference concerns the durability of response, which was shorter in the study of CART-BCMA in multiple myeloma. In studies of CAR T-cell therapies in other malignancies, a complete remission lasting for 3 to 4 months tended to continue for the long-term. The relapses seen in the study of multiple myeloma may reflect the underlying biology of the disease or perhaps the patient population enrolled.

H&O How does CAR T-cell therapy compare with other novel agents in multiple myeloma?

AC We are fortunate to have many other novel drugs in development for multiple myeloma. The response rates associated with CAR T-cell therapy appear to match those seen with other therapies, but longer follow-up from the current clinical trials is needed for confirmation. A unique aspect to CAR T cells is the potential for a single treatment course to lead to a durable remission. The idea of a one-time treatment is appealing to patients, particularly when compared with continual administration of antibodies or other drugs to try to maintain remission. The ability to maintain a long-term remission will be the key factor to help determine whether CAR T cells will replace other treatments or just join them as another option in the armamentarium.

H&O What is the prognosis for patients with multiple myeloma, and can CAR T-cell therapy offer a cure?

AC Overall, the prognosis for multiple myeloma continues to improve. In fact, it is difficult to obtain updated survival rates; the available data tend to be out of date by 3 to 5 years. According to most estimates, median survival ranges from 7 to 10 years for the entire population. However, survival is highly variable. There are patients with aggressive disease who live only 2 or 3 years after diagnosis, whereas other patients may live for 20 years.

There is hope that CAR T-cell therapy can cure some of these patients, particularly if treatment is given early enough to obtain a durable remission. In addition, continued improvements in CAR design, manufacturing techniques, and lymphodepletion regimens may further optimize the next generation of CAR T-cell products for myeloma. Longer follow-up is needed to know whether patients can be cured, but there is certainly reason to be optimistic.

H&O Do you have any insights into how to facilitate the delivery of CAR T-cell therapy to more patients throughout the country?

AC An important issue for CAR T-cell therapy in multiple myeloma is that demand exceeds the available slots in clinical trials. Several clinical trials were opened in 2018, and more are expected in 2019. At least 15 trials of CAR T-cell therapy in multiple myeloma were open when I last checked on the www.ClinicalTrials.gov website. The increase in clinical trials in more centers throughout the country should lead to more opportunities for enrollment in different geographic areas, and reduce the need for patients to travel long distances.

These studies will include large registration trials. If the trials show benefit and meet their endpoints, the hope is that the FDA will approve at least one CAR T-cell therapy for multiple myeloma in the next 1 to 2 years, which should allow many more patients to obtain access to treatment.

H&O Are any other novel treatments targeting BCMA?

AC Other BCMA-targeted treatments are in development, including an antibody-drug conjugate that is showing high response rates in myeloma and moving forward in a registration clinical trial. Ongoing studies are evaluating several bispecific antibodies targeting BCMA, which work by stimulating a T-cell response against the antigen.

Disclosure

Dr Cohen reports research funding from Bristol-Myers Squibb and Novartis and consulting/advisory board participation for Bristol-Myers Squibb, Takeda, Celgene, Janssen, Oncopeptides, Kite, Seattle Genetics, and GlaxoSmithKline.

Suggested Readings

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