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The Use of CAR T Cells in Diffuse Large B-Cell Lymphoma and Mantle Cell Lymphoma

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H&O Why are new treatments needed in DLBCL and MCL?

PM Existing therapies are ineffective in a subset of patients or have toxicities that make them inapplicable to many patients. In patients with heavily pretreated diffuse large B-cell lymphoma (DLBCL) or mantle cell lymphoma (MCL), existing therapies fall quite short. Realistically, there will always be a need for new treatments for patients with DLBCL or MCL. Until there is a treatment that is able to cure all patients without toxicity, we will always be looking for a better kind of therapy.

H&O How does CAR T-cell therapy work?

PM Chimeric antigen receptor (CAR) T cells are a kind of immunotherapy. Immune cells are genetically engineered to target an antigen that is present on the tumor cells, so they are able to seek out these cells fairly specifically. These T cells then initiate an active and sustained immune response against the target cells. In the past, there have been immunotherapies that targeted tumor cells but did not sufficiently kill them, as well as agents with the potential to activate T cells that did not specifically seek out tumor cells. CAR T cells represent a clever way of accomplishing both of these goals.

H&O Which CAR T-cell therapies are furthest along in development?

PM In North America, Kite Pharma, Novartis, and Juno Therapeutics have been leading the development of CAR T-cell products for the treatment of DLBCL or MCL. These therapies target CD19. KTE-C19 (or axicabtagene ciloleucel) is from Kite Therapeutics. Novartis has CTL019. JCAR014 and JCAR017 are from Juno. All of these therapies have the potential to be approved by the US Food and Drug Administration for the treatment of DLBCL or MCL.

H&O Why might CAR T-cell therapy be effective in DLBCL and MCL?

PM CAR T cells work differently from chemotherapy, monoclonal antibodies, and targeted small molecules. For decades, chemotherapy was the primary option for these patients, and outcomes were stagnant. With the advent of anti-CD20 monoclonal antibodies, which work differently than chemotherapy, survival improved. The immunochemotherapy era lasted for approximately a decade, until targeted therapies arrived and improved the outcomes of some patients with immunochemotherapy-resistant lymphomas. The hope now is that more active immunotherapies with novel mechanisms of action might overcome resistance to existing therapies.

H&O What types of CAR T-cell therapies have been studied in DLBCL and MCL?

PM Multiple pilot studies and phase 1 trials have evaluated a variety of CAR T cells. The earliest CARs targeted a tumor antigen, mostly CD19 in the case of B-cell lymphoproliferative disorders. Then there were attempts to increase T-cell activity with the addition of costimulatory

domains, usually CD28 or 4-1BB. This is where we are with most of the products currently moving toward approval. Investigators worldwide continue to explore ways to make these therapies more effective and better tolerated, and I think it is highly unlikely that we have reached the pinnacle of CAR T-cell development.

H&O What do clinical trials of these agents suggest?

PM There have been many pilot, feasibility, and phase 1 trials with different agents. The heterogeneity of products and small patient numbers make these trials difficult to interpret. In DLBCL, there have been 2 moderately sized phase 2 trials and a dose-finding study. Results from a planned interim analysis of the ZUMA-1 trial (A Phase 1-2 Multi-Center Study Evaluating KTE-C19 in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma), which evaluated KTE-C19, were presented at the 2016 American Society of Hematology meeting. Among 51 patients with fairly heavily pretreated DLBCL and 11 patients with transformed follicular lymphoma or primary mediastinal B-cell lymphoma, the best overall response rate was 79%, with a complete response rate of 52%. In the subgroup of patients with DLBCL, these rates were 76% and 47%. The phase 2 JULIET trial (Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients) is evaluating CTL019 in patients with DLBCL and is ongoing. Results from a dose-finding trial of JCAR014 in 32 adults with relapsed and/or refractory B-cell non-Hodgkin lymphoma were published. Among patients treated first with cyclophosphamide/fludarabine lymphodepletion, the overall response rate was 72%, and the complete response rate was 50%. Among patients who received cyclophosphamide without fludarabine, these rates were 50% and 8%.

The studies share similar characteristics. They tend to include patients who are heavily pretreated and are frequently refractory to their previous therapy. The delay between collection of T cells and delivery of the CAR product is typically from 2 to 4 weeks, but can be longer and is a source of selection bias in these studies. CAR T-cell therapy induces responses in between one-half and two-thirds of patients. Approximately one-third of patients appear to be in complete response at 3 months after treatment. Among the patients with a complete response, only a minority subsequently relapse. In summary, these are selected patients who lack effective therapeutic options, and with CAR T cells, a small subset of them achieve a complete response that seems durable. CAR T cells therefore may be curing a subset of patients with what would otherwise be considered an incurable cancer.

H&O What are the associated adverse events, and how can they be managed?

PM Cytokine-release syndrome and neurotoxicity are typically seen with all types of CAR T-cell therapies. In general, studies show that approximately one-quarter of patients will experience grade 3 to 4 cytokine-release syndrome and/or neurotoxicity. The neurotoxicity can be persistent, and, occasionally, these events can be fatal.

These adverse events are worthy of serious attention not only for their severity but also because they will limit the development of these agents. After patients with acute lymphoblastic leukemia developed fatal cerebral edema during the phase 2 ROCKET trial (Study Evaluating the Efficacy and Safety of JCAR015 in Adult B-Cell Acute Lymphoblastic Leukemia), Juno halted the development of JCAR015, a CAR T-cell product that targets CD19. Fortunately for Juno, the development of both JCAR014 and JCAR017 continues, and it was the JCAR014 product that produced the results in B-cell non-Hodgkin lymphoma discussed earlier.

CAR T-cell therapy induces responses in between one-half and two-thirds of patients.

There is much left to learn about the factors related to the development of cytokine-release syndrome and neurotoxicity. The costimulatory domains, cell dose, lymphodepleting drugs, and patient characteristics may all play a role. In some cases, it appears that the factors that might improve the activity of a product also increase the toxicity. There is a common conception that CAR T cells will replace stem cell transplant in the future, but these adverse events are a major barrier that must be overcome.

There are a few important steps to consider when administering CAR T cells. Ideally, this treatment should be administered in a center with an established cellular therapy team. The entire team should undergo training to recognize and manage adverse events. Effective treatments for cytokine-release syndrome include anti–interleukin-6 therapy and corticosteroids. The timing of these treatments is important because there is the potential they could reduce the efficacy of CAR T-cell therapy.

H&O Does CAR T-cell therapy appear effective in both the frontline and relapsed/refractory settings?

PM So far, CAR T cells have been studied only in patients with previously treated lymphomas, which is appropriate for several reasons. Preparation of CAR T cells requires a significant amount of time. There are many unknowns regarding the efficacy of these agents. In addition, there are some significant potential toxicities.

That being said, if CAR T-cell therapy can cure a third of patients with refractory DLBCL, why not use it earlier? These agents could move toward the frontline setting, perhaps starting with high-risk scenarios, as we learn how to improve tolerability and as manufacturers learn how to produce them more quickly.

H&O Are there any signals suggesting that other treatments might improve outcome when used in conjunction with CAR T-cell therapy?

PM There are a few ways to conceive of sequencing CAR T-cell therapy with other treatments. There might be a treatment given before the collection of T cells that could increase the number of T cells or improve their function. Research suggests that T cells that were collected while patients were receiving ibrutinib (Imbruvica, Pharmacyclics/Janssen) might be well-suited for use in CAR T-cell therapy. It might be possible to administer another therapy that would eradicate more of the tumor, similar to the use of chemotherapy in the setting of an autologous stem cell transplant. Conditioning regimens for lymphodepletion might allow for optimal expansion and persistence of T cells. Administering an immune checkpoint inhibitor or another drug after infusion of CAR T cells might make them more active. All of these strategies are being studied in clinical trials. Whether they prove to be safe or effective remains to be seen.

H&O Are there certain patient subgroups that might benefit more from CAR T-cell therapy?

PM There are practical aspects that make some patients with lymphoma more amenable to CAR T-cell therapy. At the centers that have been researching CAR T cells the longest, one reason for the positive results is that investigators are able to select those patients most likely to benefit from treatment. Such selection criteria may include a patient's ability to donate more T cells, or disease that is easier to control or growing less rapidly.

There do not appear to be any data supporting biomarkers for response or resistance. In some studies, biomarkers such as T-cell expansion or T-cell persistence were associated with response after the infusion of CAR T cells. These factors, however, are less of an a priori biomarker but instead recognizable after the T cells were administered.

H&O How might use of CAR T-cell therapy evolve?

PM Many T-cell products are in development worldwide. For example, there are several trials of CAR T cells in China. There will likely be significant improvements in the efficacy or tolerability of these treatments. In addition, I anticipate use of other target antigens, perhaps CD30 or CD22, which may allow expansion of CAR T-cell therapy to include different types of lymphomas or even other kinds of cancers.

Disclosure

Dr Martin has served as a consultant for Novartis.

Suggested Readings

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