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Optimizing the Benefits of BCMA-Targeted CAR T-Cell Therapy in Multiple Myeloma

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H&O Why is the B-cell maturation antigen (BCMA) a good target for chimeric antigen receptor (CAR) T-cell therapy in multiple myeloma?

SL BCMA is an important target because it is highly and almost ubiquitously expressed on plasma cells. The ligands for BCMA are often found in the plasma. Binding between BCMA and its ligands results in activation and proliferation of plasma cells, which can be linked to drug resistance. BCMA is therefore a good target from the perspectives of availability and access. BCMA is also responsible for many of the harmful effects of malignant plasma cells, which can complicate sensitization to existing therapies. Interrupting BCMA signaling and using BCMA as a therapeutic target can help kill plasma cells in more than one way.

H&O What BCMA CAR T-cell therapies are available for multiple myeloma?

SL Two BCMA-directed CAR T-cell therapies are approved for multiple myeloma by the US Food and Drug Administration (FDA). The first approved agent was a compound called idecabtagene vicleucel (ide-cel; Abecma, Bristol Myers Squibb/2seventy Bio). The approval was based on results of the KarMMA trial, which evaluated different doses of ide-cel to determine safety and efficacy. The overall response rate was between 70% and 80%, with a significant number of patients achieving a complete remission or a very good partial response. In aggregate, the data show a median progression-free survival ranging from 8 to 11 months, depending on the dose.

The other recently approved BCMA CAR T-cell therapy for multiple myeloma is ciltacabtagene autoleucel (cilta-cel; Carvykti, Janssen Oncology/Legend Biotech). Cilta-cel is a new version of an older agent from the Chinese company Legend Biotech. Data for the older agent were presented several years ago at the American Society of Hematology and American Society of Clinical Oncology annual meetings. FDA approval of cilta-cel was based on results from the CARTITUDE-1 study. Treatment with cilta-cel led to an overall response rate of approximately 97%. Approximately 90% of patients achieved a very good partial response or better. At the 2-year follow-up, the median progression-free survival was not reached. Progression-free survival continues to be good for patients achieving a complete response or negative minimal residual disease.

The main side effects associated with these agents are cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). Both of these adverse events are less severe with BCMA-targeted CAR T-cell therapies compared with CD19-directed CAR

T-cell therapies. However, administration of ide-cel and cilta-cel still requires a hospital team that is experienced in the management of these potential adverse events.

Ide-cel and cilta-cel represent very exciting first steps in the cell therapy world for patients with multiple myeloma. They have led to significant treatment-free intervals and high response rates in patients with refractory multiple myeloma.

H&O How does the efficacy of BCMA CAR T-cell therapies compare with other treatments used in multiple myeloma?

SL The most common treatments in refractory multiple myeloma are daratumumab (Darzalex, Janssen Oncology), carfilzomib (Kyprolis, Amgen), pomalidomide (Pomalyst, Celgene/Bristol Myers Squibb), lenalidomide, and bortezomib. These therapies are associated with response rates of 30% to 40% in the refractory population. In comparison, the BCMA CAR T-cell therapies are associated with response rates of 70% to 90%. These compounds are highly effective compared with the other available drugs. There is such excitement about these new treatments not only because they offer a novel mechanism of action by targeting BCMA, but also because they are highly effective. We hope that these benefits will translate into long-lived antitumor immunity. Longer follow-up will be needed for confirmation.

Some physicians have raised the idea of collecting T cells earlier in the course of the disease, possibly at diagnosis.

H&O What are the advantages and challenges in using BCMA CAR T-cell therapy in multiple myeloma?

SL An advantage is the high expression of BCMA, which is expressed by many different cells. Ide-cel and cilta-cel are low-risk therapies from a toxicity perspective. A common question that is being addressed in current trials is how well these treatments compare with transplant. Transplant is typically not an option for patients older than 78 or 79 years. In contrast, physicians are beginning to use CAR T-cell therapy in patients older than 80 years who have a good performance status.

Access to ide-cel and cilta-cel is a challenge. It is currently a struggle to ensure there are enough manufacturing slots for all patients who need this treatment. Another challenge concerns persistence of the CAR T cells. In the past 2 decades, management of multiple myeloma was based on a model of continuous therapy, which is capable of controlling low-level disease. I and others have noted that in many cases, once the CAR T cells start to disappear, the clock starts ticking on the development of relapsed disease. The next set of challenges are to understand how to maximize persistence and maintain long-term antitumor immunity after the CAR T cells leave the body.

H&O Are there ways to improve the efficacy of BCMA CAR T-cell therapy in multiple myeloma?

SL In multiple myeloma, we typically do not administer an active agent by itself. For the future, 2 strategies are worth revisiting. The first is a maintenance strategy. Is there a treatment we can administer after the infusion of CAR T cells—at or near the time the cells start to wear off—in order to prolong the duration of efficacy? This strategy would not follow a continuous maintenance model like the current one. Instead, the duration of treatment would be short, but would last long enough to provide coverage of an antitumor effect to eradicate the residual clone and ultimately result in a cure. Understanding how to do that will be an important next step in the management of these patients.

The second strategy worth revisiting is how to improve the quality and health of a patient's T cells before they are collected. Some physicians have raised the idea of collecting T cells earlier in the course of the disease, possibly at diagnosis. Another interesting question would be whether there are immune adjuvants that could be used prior to apheresis to enhance the number and quality of T cells that are extracted from the patient. Concepts such as this one are beginning to be tested. They may involve short-duration immunomodulatory agents or short-duration immunostimulants, treatments that are known to activate T cells to make them more potent than the T cells typically present in patients with refractory multiple myeloma.

H&O Which types of patients with multiple myeloma are candidates for BCMA CAR T-cell therapy?

SL Currently, the candidates for CAR T-cell therapy are those who fit the FDA indication: they have received 4 or more prior lines of therapy and they have a good-enough

performance status to tolerate CRS or neurologic toxicity, should these adverse events arise. It is important to recognize that this eligibility differs from that for transplant, given that older or frailer patients may be considered for CAR T-cell therapy despite being excluded from transplant eligibility. BCMA CAR T-cell therapy appears to be less intense than transplant in terms of toxicity, and more patients may be eligible for it than for transplant.

There are ongoing clinical trials in which CAR T-cell therapy is administered earlier in the disease course, in first relapse and in newly diagnosed patients. Other trials are comparing CAR T-cell therapy vs high-dose therapy and transplant. These trials are addressing important questions to help us understand how to best incorporate CAR T-cell therapy into routine care.

H&O Do you have any recommendations regarding the use of BCMA CAR T-cell therapy in patients with multiple myeloma?

SL Early referral is key. Physicians at CAR T-cell therapy centers should learn of patients earlier in their disease course. By the time that patients have received 4 lines of therapy, they have triple-class refractory disease and poor blood cell counts. We want to see the patient well before that point, so that we can begin the process of planning treatment and slotting allocation. It is necessary to ensure that a patient's performance status is good enough to allow treatment with a CAR T-cell therapy. These aims are best served by identifying patients earlier in the disease course. Early referral also allows us to minimize disease burden, to a certain extent. Decreased tumor burden at the time of CAR T-cell infusion can lower the risk of severe CRS and severe ICANS. These steps are critical to maximizing the number of patients who can receive CAR T-cell therapy and to optimizing the benefit of treatment.

Disclosure

Dr Lonial has served as a consultant for Amgen, Novartis, Bristol Myers Squibb, Janssen, Celgene, AbbVie, Genentech, GlaxoSmithKline, Takeda, and Pfizer; has received clinical research support from Takeda, Janssen, Novartis, and Bristol Myers Squibb; and has served on the board of directors (with stock) of TG Therapeutics.

Suggested Readings

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