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Advances in Off-the-Shelf CAR T-Cell Therapy



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H&O What is the manufacturing process for approved CAR T-cell therapies?

RB Currently, the US Food and Drug Administration has approved 2 chimeric antigen receptor (CAR) T-cell therapies: axicabtagene ciloleucel (Yescarta, Kite) and tisagenlecleucel (Kymriah, Novartis). Both are autologous CAR T-cell products, and their preparation involves several steps. First, patients undergo apheresis to collect T cells. These T cells are activated in the laboratory and then transduced with a viral vector, which introduces the CAR into the cells. The cells go through a period of expansion, and then they are frozen down. They are infused back into the patient following lymphodepleting chemotherapy.

The manufacture of one of the autologous products takes approximately 28 days, although it can take as little as 14 days. The manufacturing process can be labor-intensive and expensive. There is a significant variation in the amount of product that is generated from patient to patient. There are also variations in the manufacturing processes; some use lentiviral vectors and others use retroviral vectors to insert the CAR into the T cell. Both techniques have advantages and disadvantages.

H&O What are the typical response rates and adverse events associated with the currently approved CAR T-cell therapies?

RB Tisagenlecleucel is approved for B-cell acute lymphoblastic leukemia in pediatric and young adult patients ages 25 years or younger, as well as adult patients with lymphoma. In the pediatric patients with B-cell acute

lymphoblastic leukemia, the response rate is approximately 90%, which decreases to approximately 60% a year after treatment. Among patients with lymphoma, approximately 40% have a complete response 3 to

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6 months after treatment. Axicabtagene ciloleucel, which is approved for diffuse large B-cell lymphoma, has a similar rate of complete response.

The main adverse events for most of the CAR T-cell therapies are cytokine release syndrome, neurotoxicity, infections, and prolonged cytopenia.

H&O Why is there interest in creating off-the-shelf CAR T-cell technology?

RB The main reason for the interest in off-the-shelf CARs is that preparation of the autologous product requires that patients are well enough to have their T cells collected. Patients must be stable for approximately a month before the cells can be manufactured

and returned. Patients must also have a certain minimum number of T cells to start with.

There is substantial variation among every single product that is manufactured. With an off-the-shelf product, it is not necessary to collect T cells from each patient. The product is premade and ready for administration when needed. A patient with very aggressive disease may still have enough time for treatment with off-the-shelf CARs. Off-the-shelf CARs are made from cells from healthy volunteers, and they may be more effective than a product that is generated from cancer patients, whose T cells may be defective. T cells from healthy volunteers are more likely to be normal.

Another potential benefit involves cost. An autologous program requires a huge logistic exercise to collect cells from a patient through apheresis, send the cells to a manufacturing site, manufacture the product, and then return it. With an off-the-shelf product, in theory, it should be possible to scale up, so that a single healthy volunteer can generate enough cells to treat multiple patients. Overall, we would expect the cost to decrease compared with the autologous program.

H&O What does preliminary research of this technique show?

RB A key aspect of generating an off-the-shelf CAR is removal of the endogenous T-cell receptor that is normally in T cells. Otherwise, the infused T cells would attack the patient. There are several different techniques to delete the endogenous T-cell receptor: transcription activator-like effector nucleases (TALEN) technology, clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9, and zinc-finger nucleases. After the T-cell receptor is removed, the CAR can be introduced. These cells are then expanded and frozen down as an off-the-shelf product.

H&O What clinical trials have evaluated off-the-shelf CAR therapy?

RB The off-the-shelf CAR T-cell product known as UCART19 targets CD19. The TALEN technology is used to knock out the endogenous T-cell receptor. UCART19 has been studied in adult and pediatric patients. The first-in-man, dose-escalation phase 1 CALM trial (UCART19 in Advanced Lymphoid Malignancies) is the first study of an off-the-shelf product in adult patients with relapsed adult B-cell ALL. The PALL trial (Pediatric Acute Lymphoblastic Leukemia) is evaluating UCART19 in pediatric patients with acute lymphoblastic leukemia. The CALM trial is testing 3 different dose levels. The study is currently under way at dose level 3. The early response

rates with dose levels 1 and 2 were encouraging. In dose level 1, we infused a cell dose that is approximately 1 log lower than what is used in autologous studies. Interestingly, there was very good cell expansion and efficacy at this dose. Another interesting finding is that repeat infusions led to responses. The PALL study is testing a fixed dose.

Data from a pooled analysis of the CALM and PALL trials were presented at the 60th American Society of Clinical Oncology meeting. Among 21 evaluable patients, the rate of complete response/complete response with incomplete recovery of counts was 67%. This rate was 82% among patients who underwent lymphodepletion with cyclophosphamide, fludarabine, and alemtuzumab (Campath, Genzyme). There was no UCART19 expansion and no responses among the 4 patients who received lymphodepletion with only cyclophosphamide and fludarabine. Minimal residual disease (MRD)-negative status was reported in 71% of patients. Redosing with UCART19 resulted in cell expansion and MRD-negative status in 2 of 3 patients.

The toxicity with UCART19 was similar to that seen with the autologous CAR T-cell therapies. Patients developed cytokine release syndrome, and there were some reports of neurotoxicity. There were few reports of graft-vs-host disease, which would be expected to occur more often with an off-the-shelf product vs an autologous product.

Evaluation of UCART19 is ongoing in adult and pediatric populations.

H&O What are the next steps needed in the development of off-the-shelf CAR T-cell therapy?

RB A drawback of off-the-shelf CARs is that the cells do not persist for long enough. In the autologous setting, CARs must persist for maximum efficacy. With off-the-shelf CARs, the expectation is that these cells will be rejected more rapidly and will lack persistence because they are from a third party. It will be necessary to improve the persistence of off-the-shelf CARs, possibly by knocking out parts of the major histocompatibility complex of the T cells. This alteration will prevent the host immune system from recognizing the CAR T cells, and therefore they will avoid rejection and persist longer.

H&O Do you have any recommendations for the use of CAR T-cell therapy in the clinic?

RB CAR T-cell therapy is an exciting technology that works well in some hematologic malignancies, particularly B-cell acute lymphoblastic leukemia and B-cell lymphoma. It is important to note that there is some significant associated toxicity, but the centers that deliver

this therapy are fully trained to manage it. Administration of CAR T-cell therapy requires a close working relationship among the treating hematologists, physicians in the intensive care unit, neurologists, and renal physicians to ensure the patient's safety throughout treatment.

H&O Do you have any insights into how this therapy might evolve?

RB So far, the main success in this area has been with CD19-targeted CARs in B-cell malignancies. The next step is to apply the CAR T-cell technology to other diseases. There are some exciting data in multiple myeloma, where the B-cell maturation antigen (BCMA) is a target. Patients with other blood cancers, such as acute myeloid leukemia, are also being treated in clinical trials. The ultimate goal would be to expand treatment to solid tumors. These cancers would be more challenging to treat with CAR T-cell therapy, but the field is heading in this direction.

Disclosure

Dr Benjamin has received research funding from Servier and Pfizer. He has received honoraria from Amgen, Takeda, Novartis, Gilead, and Celgene.

Suggested Readings

Benjamin R, Graham C, Yallop D, et al. Preliminary data on safety, cellular kinetics and anti-leukemic activity of UCART19, an allogeneic anti-CD19 CAR T-cell product, in a pool of adult and pediatric patients with high-risk CD19+ relapsed/refractory B-cell acute lymphoblastic leukemia—a pooled analysis of the CALM and PALL phase 1 trials [ASH abstract 896]. *Blood*. 2018;132(suppl 1).

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