What Role Does Cell Source Have in the **Future of Immune Cell Therapies?**

The future of cellular therapies likely holds possibilities beyond just allogeneic versus autologous.

By Leah lawrence
Contributing Writer

Cellular therapies like autologous chimeric antigen receptor (CAR) T-cell therapy are revolutionizing cancer treatment.

"These therapies offer a new approach to treatment that is independent of radiation and chemotherapy, and have the capability of targeting tumor cells — or any target cell — very specifically," said Adrian P. Gee, PhD, director of the Clinical Applications Laboratory, Center for Cell and Gene Therapy, Baylor College of Medicine. "It gives a degree of specificity that wasn't there before."

Like something out of science fiction, CAR T-cell therapy involves taking T cells from a patient's blood, editing those T cells to express a CAR to recognize a specific antigen, growing those cells in the laboratory, and returning them to the patient to bind to cancer cells and kill them.

The first clinical trial of an experimental CAR T-cell therapy began in 1997, and, as of early 2022, six commercially produced CAR T-cell therapies have been approved by the United States Food and Drug Administration for diseases including aggressive B-cell lymphoma or mantle cell lymphoma, acute lymphoblastic leukemia, follicular lymphoma and multiple myeloma.[1,2] Most recently, FDA approved axicabtagene ciloleucel for the first-line treatment of relapsed or refractory large B-cell lymphoma,[3] beginning what is likely to a new era of seeing these therapies used in earlier lines of treatment.

Autologous Limitations

Ongoing work is being done to provide access to immune cell therapies to as many patients as possible in North America and around the world, explained Bruce L. Levine, PhD, the Barbara and Edward Netter Professor in Cancer Gene Therapy at the University of Pennsylvania Perelman School of Medicine.

"In the indications where we have approval it may only be about 20% of eligible patients that are able to access the therapies for reasons of referral, awareness, eligibility or other reasons," Levine said.

Some of these limitations are a result of the autologous nature of currently available therapies. For example, the timing of CAR T cell administration — which must include time to collect, manufacture, test and deliver the cells — can take weeks.

"While they wait, patients may need intervening therapy and may not be well enough to receive the cells even once the cells are ready," Levine said.

Other eligible patients may not have enough cells or the right cells to be able to successfully go through apheresis, or the cells obtained may not be healthy enough to expand in the lab.

Layered on top of these issues are concerns related to cost, geography, access and manufacturing and supply chain issues.

Allogeneic Appeal

For these reasons and others, there is growing interest in the development of allogeneic cellular therapies — sometimes referred to as "off-the-shelf" products. The primary difference between autologous

and allogeneic products is the source of the cells.

"Autologous therapies have the benefit of being tailored to an individual and the patient has the benefit of being, by definition, an HLA match," said David McKenna, Jr, MD, professor and American Red Cross Chair in Transfusion Medicine at the University of Minnesota Medical School. "Not all patients will be healthy enough to qualify for the therapy though."

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Allogeneic therapies would be developed from healthy donor cells rather than from patients who have been exposed to prior treatment. That means that certain patients who may have been ineligible for autologous therapy, for example, because of low-quality T cells, may qualify for an allogeneic product.

"The variability and various quality parameters for starting material can be quite huge with autologous therapy," said McKenna. "In contrast, if you are able to find a suitable donor — whatever that might mean in each case — you could theoretically make enough product, freeze it down and use it to treat tens or hundreds of patients with the same cell therapy product."

A variety of sources for allogeneic products are being explored, including the use of peripheral blood mononuclear cells, cord blood and pluripotent stem cells.

Although allogeneic products are not as far along in clinical development as autologous ones, progress is ongoing. Results from a phase 1/2 study of cord blood-derived natural killer (NK) cells were presented at the 2022 American Association for Cancer Research (AACR) Annual Meeting. In the study, the NK cells were activated and complexed with a CD30/CD16A bispecific antibody (AMF13) and used to treat patients with relapsed or refractory CD30-positive lymphoma. The study included 22 patients treated across multiple dose levels. The overall response rate was 89% with 53% of patients having complete response and 37% having partial disease response.[4,5] Among those treated at the recommended phase 2 dose, the overall response rate was 100%.

Another company presented preclinical results of an allogeneic, anti-BCMA, CAR T-cell therapy in development for relapsed or refractory multiple myeloma. Data demonstrated that the product was cytotoxic against BCMA-expressing tumor cells and had in vitro characteristics suggestive of resistance to killing by allogeneic T cells and NK cells.[6]

Allogeneic products are not without potential risk including immunological reactions. Depending on the cell type and desired effect, patients may require immune suppression to avoid rejection of the new cells. However, work is being done to minimize the potential for reactivity.

"These allogeneic products are not from an identical twin," Levine said. "The long-term persistence for the first 28 days and beyond is likely not be as robust as engraftment as we see with autologous products."

Levine added that it remains to be shown how long cord blood-derived or healthy donor-derived cells can be expanded.

"The longer you expand those cells in the lab to make more cells and more doses, the more 'exhausted' or differentiated they will become," Levine said. "If by expanding to make more doses we move to a phenotype that may be more exhausted, it may not have the potency needed."

Cost & Manufacturing

The potential for cost savings is another reason that allogeneic therapies hold appeal.

Drug acquisition costs for autologous CAR T-cell therapy range from $373,000 to $475,000 depending on the drug and indication. Additional expenditures, such as lymphodepletion, imaging, bridging therapy and facility costs, have the potential to drive the total cost of care up to $1 million.[7]

"There is huge potential for cost savings and efficiencies with allogeneic therapy over autologous therapy," McKenna said.

However, Levine noted that if subsequent therapies including hematopoietic stem cell therapy are required after allogeneic therapy, the cost savings may not be as great.

There are also manufacturing issues innate to autologous treatment. For example, CAR T-cell therapy

requires a gene therapy manufacturing process, often including viral vectors. T cells must be collected, genetically modified, expanded, stored and prepared for infusion.

During the pandemic, some of these issues were exacerbated by supply chain issues.

"For cellular therapies, in general, there are a lot of supplies," Levine said. "There are things like reagent materials or filters for manufacturing vectors that go into the process and there have been significant back orders. That impacts the ability to manufacture these products."

In 2021, Bristol Myers Squibb reported that demand for its multiple myeloma CAR T drug was outstripping capacity. Because this therapy is personalized to each patient, the manufacturer had to reserve manufacturing slots for each patient's therapy. The company also reported problems in the supply chain of viral vectors.[8]

"If we are talking about a wide-scale disease like certain leukemias, these allogeneic products could be readily, commercially available," Gee said. "Companies may be able to set up large banks of cells."

Additional Considerations

Advances in CAR T and other cellular therapies represent a significant area of growth and expansion for transfusion medicine.

"With the kind of increase we've seen in immune cell therapies across the board, and with apheresis as the starting material, apheresis centers have seen a large increase in activity for this type of collection," McKenna said.

Currently, each commercially available product has its own expectations for how cells should be collected, labeled, and transported.

"For something that a lot of apheresis units are used to doing, it can be kind of burdensome," McKenna said.

As the number of products increases, more work is needed to standardize to ensure a high-quality product as well as to facilitate widespread access to the cellular collections that end up becoming these products, according to Eric A. Gehrie, MD, executive physician director, Direct Patient Care & Emerging Cell and Gene Therapy Offerings, American Red Cross.

"We need to determine how the collections should occur, in order to support the development of the best possible autologous and allogeneic products," Gehrie said.

In a paper published in 2020, Andrew D. Fesnak, MD, of the Perelman School of Medicine at University of Pennsylvania, described this lack of standardization as an "inherent tension in academic cell manufacturing".[9]

"The mechanism of apheresis collection and the specific clinical features seen in these patients combine to generate apheresis products with high variability of content," Fesnak wrote. Standardization would allow for a robust process for scaled-up and scaled-out manufacturing that would be necessary to produce "off-the-shelf" products.

Gehrie said that a lot of attention in cellular therapies research is focused on the gene editing, cellular engineering or the dosage. There also would be many practical benefits to the development a centralized approach to oversight and administration of apheresis collections, he said.

"Any product that starts with apheresis collection — whether autologous or allogeneic — the way the apheresis is performed could potentially alter the product collected, which could impact the outcomes of patients that go on to receive that product," Gehrie said. "At the same time, we need to make sure that patients have access to an apheresis center that is able to collect the product that they need. To do this, we need to also be working toward the development of an optimal collection technique, or, a small suite of techniques that address downstream manufacturing needs while also

ensuring that apheresis centers can focus on developing a manageable number of procedures. In these ways, standardization could help to ensure product quality as well as improve access to the treatments."

The More the Merrier

All of these considerations and more have to be included when thinking about the future of cellular therapies, which most agreed will likely include both autologous and allogeneic products.

"If allogeneic can be shown to be successful in a wide range of diseases, that would probably become the therapy of choice because of rapid availability and the healthy nature of the cells," Gee said.

On the flip side, though, autologous will almost definitely remain at least a niche therapy, Gee added. There will always be a need for autologous transplant in diseases where there is potential for reactivity if an allogeneic donor is used, or where there is not a sufficient number of patients for allogeneic therapies to be commercially attractive to produce.

"We are going to have allogeneic and autologous," Levine agreed. "In some cases, there may even be a direct donor. If a patient has already had a stem cell transplant, we may go back to the healthy donor to generate CAR T cells."

For many pediatric patients that have already received an allogeneic stem cell transplant and their leukemia has returned, their leukapheresis cell collections are composed of donor derived T cells, he said.

The future likely also holds new technologies and approaches, such as in vivo CAR T-cell gene therapy. Currently, in vitro CAR gene delivery in autologous T cells is mainly through lentiviral vectors. In vivo induced CAR T cells could use nanotechnology to "encapsulate CAR encoding genes into nano-delivery systems … which are then targeted to tumor regions in vivo to edit T cells in situ at tumor sites."[10]

More and more data are coming out for hematologic malignancies and solid tumors.

"The idea of moving into more engineered cellular therapies that would enhance the efficacy and reduce the toxicity of cancer treatment is a very promising next step for the field, it is our responsibility to follow through on the potential and help to make it a reality for patients" Gehrie said. ■

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