APPLIED CLINICAL TRIALS

Facilitating Adoptive Cell Therapy Clinical Trials

By Fiona Thistlethwaite, Panteli Theocharous | December 9, 2020

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Adoptive cell therapies are live biological platforms that leverage the human immune system with cells engineered to attack specific target cells (most often cancer cells) for an extended period of time. The leading approach involves chimeric antigen receptor T cells (CAR-T) for the treatment of hematological malignancies. Initial successes with several of these drugs are driving the development of many more cell therapies and consequently increasing movement of candidates into the clinic. This is also predicated on findings from the early days of immunotherapy, specifically bone marrow and stem cell transplantation.

Much research is focused on finding mechanisms for delivering activated T cells through the tumor microenvironment and into solid tumors, which account for approximately 90% of diagnosed cancers. Evolving technologies include modification of other receptors on T cells to better target tumor microenvironments and minimize off-tumor cross-reactivity.

Adoptive cell therapies comprise one of the largest classes of novel immunotherapies, and many companies now have an interest in adoptive cell therapy in the solid tumor setting. Treatments based on tumor-infiltrating lymphocytes (TILs), which require surgical tumor resection combined with cell therapy, and natural killer (NK) cells also are attracting attention. Most of the adoptive cell therapies in the pipeline are autologous therapies, which use a patient's own cells that are cultured, engineered and expanded outside of the body before being reintroduced to the patient, but allogeneic or off-the-shelf approaches using donor cells are being investigated as well.

Specialized therapies with unique challenges

These very specialized therapies require significant infrastructure and coordination and come with associated challenges and costs. Recruiting study participants for highly experimental treatments can be difficult. It is relatively rare to find patients who meet the specific genetic and other criteria who are fit enough to withstand the potential significant toxicities associated with intensive chemotherapy conditions and cell therapy. These patients are typically multiply relapsed but still immunocompetent.

The field is still at the stage where a key requirement is to show efficacy—even if this is only in highly selected patient groups. It is the norm for therapies early in development to be assessed in patients far along their journey (i.e., where proven therapies have been exhausted). If efficacy can be proven in this "hard-to-treat" group, the treatment can be moved to an earlier line of therapy (as is happening now with CD19 CAR-T) and strategies to reduce toxicity and make it more broadly applicable can follow. Cell therapy is so complex and has potentially severe toxicities, so the type of patient we are presently looking for has PS 0 or 1, little comorbidity and likely to be in the younger age category (i.e., < 70). Individual trials will define the exact eligibility criteria.

Once a patient is identified and has agreed to participate, cells need to be harvested—generally by apheresis for CAR-T approaches or surgical resection for TIL therapy. Not all surgeries are the same, and the clinical trial infrastructure can be challenging to coordinate.

The cell therapy is then manufactured at another location, which could be nearby or across the globe. Regulations also are complex and incompletely harmonized on the international level, so they can vary depending on where the tissue sample is procured and manufactured.

When the cell therapy is delivered back to the trial site, coordination with the patient's conditioning chemotherapy is necessary before administration, which is particularly challenging during a pandemic.

During treatment, a range of expertise integrated via a multidisciplinary approach is needed to ensure the entire process goes smoothly. For cancer patients, that includes at a minimum the oncologist, a hematology team, an

infectious disease specialist and potentially a critical care team to respond if cytokine release syndrome or other issues occur.

Once the patient is discharged, extended follow-up is necessary because these therapies involve genetically modified materials and are intended to provide durable remission. Infrastructure is needed to follow patients for many years after treatment.

Overcoming bottlenecks in the vein-to-vein supply chain

Finding patients for cell therapy clinical trials generally requires establishing the right networks to identify suitable patients willing to consider participation. Patient referral pathways are particularly valuable when recruiting for studies involving rare indications, including larger academic centers of excellence where these patients are already being treated and where established patient advocacy groups exist.

Autologous cell therapies require a unique vein-to-vein supply chain, beginning with a collection of cells from the patient and ending with reinfusion of the modified cells. For sample collection, limited apheresis capacity due to increased activity in the transplant setting is an issue and is driving investments to build additional capacity. For trials that require surgical sample collection, engagement with multiple institutions is often essential to enable access to a range of sample types (e.g., skin, lung).

Close collaboration with CROs offering clinical logistics services with experience supporting cell therapy trials is invaluable for addressing the logistical challenges associated with timely delivery of initial samples and the ultimate cell therapy products with an assured chain of identity. With continued clinical outsourcing anticipated, experienced CROs will have an important role to play, particularly in relation to managing logistics and associated scalability.

On-site, comprehensive training and oversight is required for storing and dispensing these complex drugs once they are returned from the manufacturer. Training of doctors, nurses and site staff is vital for appropriate delivery of the cells and management of toxicity and any side effects.

Overall, the ideal cell therapy trials have an established framework that ensures management of logistics, good communication and orchestration of the process on a per-patient basis. Systems are designed to assure the appropriate level of attention to detail when it comes to process flow, IP, chain of custody, cold chain and related considerations. Optimizing logistics is not just about securing resources and manpower; it involves implementing processes that facilitate measuring and monitoring to ensure these live biological therapies are closely tracked throughout the entire process.

As adoptive cell therapies advance from early phase trials into Phase II and III, scalability within this framework will need to be addressed. Electronic measures for careful tracking throughout the supply chain and increased efficiency will be important elements of future solutions. The hope is that CROs with growing expertise in cell therapy and broad experience leveraging a range of digital capabilities across phases of development, will be increasingly able to ascertain and apply relevant solutions to enhance scalability.

Need for centers of excellence

In the short term, adoptive cell therapy trials will take place in larger centers of excellence with the capabilities and facilities required to run complex studies and to manage patients through the multidisciplinary process. These centers or hubs draw local referrals when possible to limit travel burdens on patients.

However, these centers of excellence are presently limited in number and capacity and can become saturated with clinical trial requests. To expand patient access, it will be essential to bring the experience of leading academic teaching hospitals into community-based hospitals and centers that may not be conventionally involved with adoptive cell therapy trials or treatments on a regular basis. Although community-based hospitals may not be in a position to treat patients on complex protocols, they have an important role to play in prescreening and referring appropriate patients.

Breaking down silos with integrated end-to-end support

The cell and gene therapy ecosystem is complex, so all stakeholders must learn from one another to continue to refine processes. We need to build networks that include key opinion leaders at academic centers and incorporate higher levels of engagement, continuity and consistency in executing these trials.

This type of non-siloed approach is best supported by comprehensive, end-to-end support from global clinical trial service providers with real experience in adoptive T cell therapies offered in a personalized and bespoke manner, with deep understanding of the nuances of the technology and the ability to translate that understanding into practical operational solutions.

Such comprehensive solutions include early engagement and consultative support of regulatory documentation, CMC data and manufacturing strategy development to ensure streamlined transition into the clinic. The key is to be proactive and implement best practices that simultaneously allow greater efficiencies while ensuring safety and compliance and facilitating patient engagement throughout the patient journey. Remaining agile around

the applications of technology, from digital or telemedicine to wearables, aids leveraging all parts of the business to ensure continuity for the patient and the process.

Patient-friendly data collection

Because adoptive cell therapy patients receive intensive treatment for 14 days or more and are subsequently monitored for years, there is a tremendous volume of clinical data collected. To make that data collection as patient-friendly as possible, innovative and flexible approaches are being employed.

While in the hospital, real-time data visualization of cytokine levels, blood count, liver activity and other biomarkers is critical. That level of scrutiny is not typically required during the follow-up period, allowing for use of other more patient-friendly methods of data collection.

There is increasing interest in implementing the ambulatory care model for complex cell therapy trial patients. New patient-centric tools and technologies for data collection and analysis will be essential for successful implementation of decentralized trials, including self-collection of blood samples and algorithms that monitor and identify early signs of excess cytokine release. Wearable technologies that continuously monitor temperature, blood pressure, pulse rate, oxygen saturation, and other data also will be key enablers of the outpatient approach.

The goal is to minimize the burden on the site and the patient and simplify the complexities of adoptive cell therapy trials, not only for early-phase studies, but also for medicines as they enter registration studies and even at the standard-of-care stage. Technological/digital innovations will be particularly impactful for longer-term follow-up of patients, a time in which data collection falls both within and outside of standard of care. The collection of long-term patient-reported outcome measures, for instance, is crucial to understanding not only health economics, but the effect of the treatment on quality of life.

Improving the patient experience

Patients who receive personalized adoptive cell therapies may experience tremendous anxiety. We need to recognize, appreciate and understand what patients are going through from the initial treatment process through long-term follow-up. Their voices should be brought into the trial development process as early as possible, and mechanisms should be in place for engaging with patient advocacy groups and other external stakeholders to incorporate their input. Contingencies must be built into clinical studies to ensure patient engagement is realized and validated.

An example of an area needing improvement is the information provided to subjects considering participation in an adoptive cell therapy study. Initial, unpublished surveys from a patient focus group we conducted in Manchester have revealed that patients considering participation in a CAR-T trial, initially want simple information. Some patients seek additional technical discussion, while others do not. Typically, information sheets given to patients are 30-40 pages long and are technically dense. It is difficult for patients to tease out the really important points they need to consider. One possible solution would be to provide the information electronically, with basic information provided on a home page and a menu of options where patients can access other, more detailed technical information, if desired.

Network approach in the UK

The landscape for cell therapies in the UK is supported by a countrywide network of Innovate UK (IUK)-funded centers—the Advanced Therapy Treatment Center (ATTC) Network)—that share best practices and learnings. This approach has allowed the scale-up of trial activity in a way not possible for individual institutions. Each of the centers works with commercial, clinical and academic partners and draws together programs of activity.

The center in Manchester (iMATCH—the Innovate Manchester Advanced Therapy Center Hub) has two clinical partners across seven different hospitals and covers adult and pediatric oncology and hematology, as well as different cell and gene therapies in the oncology and non-oncology settings. In addition, an active education program, offering higher-level degrees as well as E-learning for healthcare workers and allied professionals is available as part of the construct.

While each center has its own approach, The Christie NHS Foundation Trust in Manchester has elected to establish the Advanced Immunotherapy Cell Therapy (AICT) Team, which is focused on solid tumors. The team is tumor agnostic and focuses on cell therapy trials, which has enabled the setup of infrastructure within the organization and focus on delivery at scale.

Participating in the overall ATTC Network has opened up communication pathways with regulators and working with the health authorities to establish road maps to share experience across the network and to establish third-party agreements and license extensions.

Goals for the future

The future is certainly exciting for adoptive cell therapy clinical trials. Technological innovations are being pursued that will lead to highly impactful therapies engineered with minimal toxicity and enhanced efficacy. Gene-delivery technologies also will likely evolve and expand to include non-viral methods, such as gene-editing/CRISPR, and potentially move toward chemical or physical technologies and away from viruses completely.

Research in this area aims to address concerns about unintended consequences of using viral agents and to potentially eliminate the need for long-term follow-up.

Most therapies today are personalized, autologous medicines. Allogeneic, off-the-shelf products are an attractive alternative that eliminate many of the procurement and logistics issues associated with autologous treatments. The challenge is to develop allogeneic solutions that do not reduce efficacy or increase toxicity. Introducing allogeneic cells into patients will result in toxicity shifts, and multidisciplinary teams still need to be in place to manage these complex toxicities. Understanding differences in the cost of goods for process development and manufacturing is important, as is scalability and the potential to bring these life-changing therapies to a broader patient pool. Given the level of research in this field in both academia and industry, we can expect allogeneic products over the medium term.

Process development will be the key to success for autologous therapies. Manufacturing capability and clinical development must be more aligned and synchronized to realize optimum capability and scalability and thus capacity. Ultimately, to minimize complexity and ensure consistency, we may see CROs offering a full suite of clinical development services in conjunction with process development and manufacturing support. This also may afford the opportunity to transition from the larger academic teaching hospitals and centers of excellence—leveraging their experience—toward treating patients in community settings. Broadening the patient pool remains an aspiration for patients with unmet needs for these potentially transformative therapies.

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