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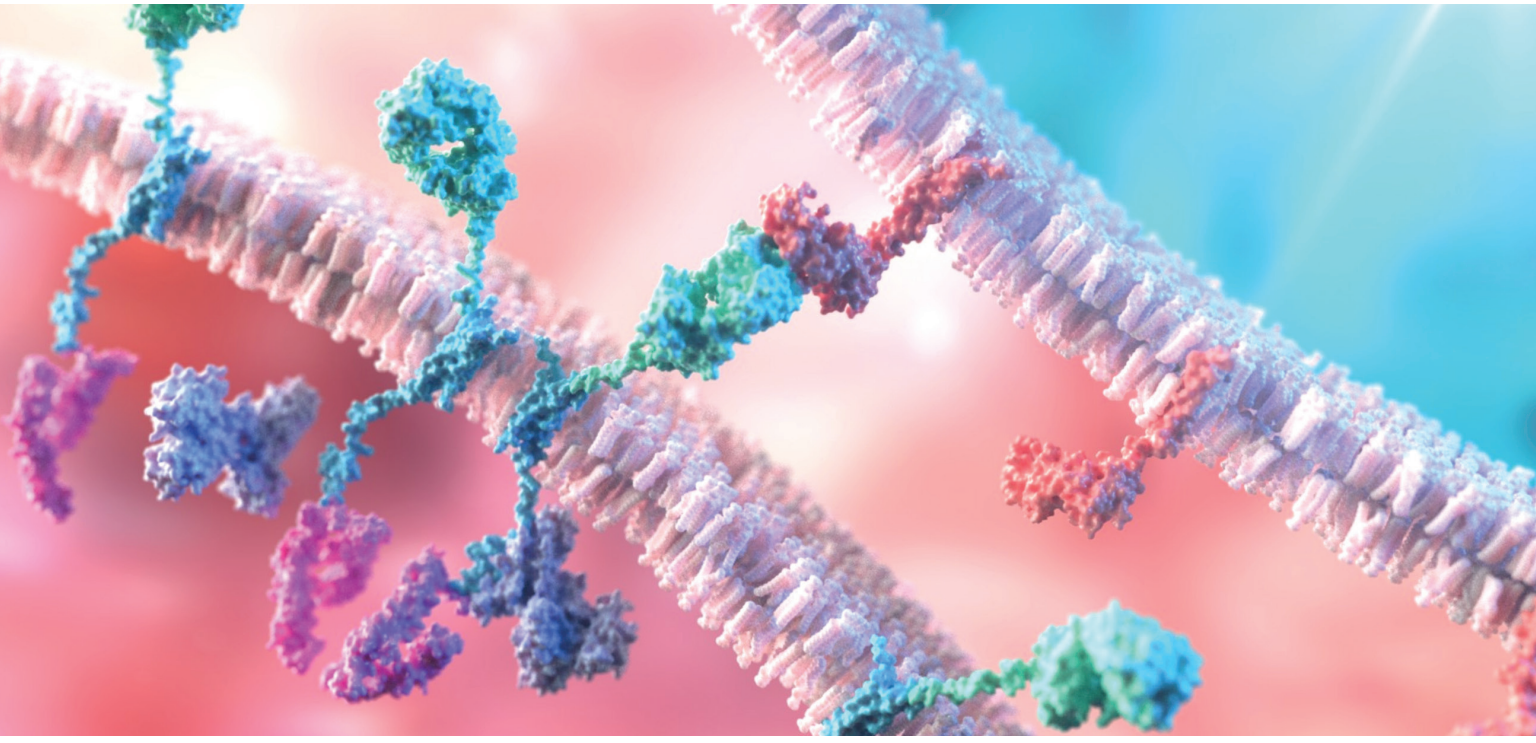
CAR-T Cell Therapy in Clinical Trials

The importance of CAR-T cell therapy in clinical trials: the industry's evolving, maturing focus



Global drug developers in partnership with leading scientists have sharpened focus on advancing the development of CAR-T therapies, expanding applications and improving key logistics of this evolving therapeutic field. In turn, we are seeing three major themes emerging in global discussions about CAR-T in 2020.

SEEKING MORE SOPHISTICATED CAR ENGINEERING FOR SOLID TUMORS

CAR-T therapeutics continue to drive the paradigm shift of therapies for patients who are at the end of treatment options for hematological malignancies ranging from palliative to potentially curative. Antigens for CAR-T in liquid tumors are fairly well defined compared to solid tumors, which are much less defined. Therein lies the clinical challenge of translating liquid tumor experience to solid tumor applications. The data supports the need for more sophisticated and scientific engineering of the CAR.

Global medical professionals acknowledge the broad potential of CAR-T cell therapy. To date, it has been validated in relapsed and refractory B-ALL malignancies, while the current clinical responses in solid tumors have been sporadic. Solid tumors are a challenge for multiple reasons including:

- Lack of antigen specificity;
- Poor trafficking and expansion;
- Hostile immunosuppressive microenvironment;
- Tumor escape and relapse;
- Toxicity of CARs; and
- Time-consuming and expensive manufacturing of CAR-T cells.

Given the limitations of current CAR-T cell therapy, sophisticated strategies are under investigation to overcome them. They include:

- Targeting multiple tumor antigens to lessen antigen escape;
- Harnessing immune checkpoint inhibitors to increase effector response;
- Using next-generation CAR-T cell engineering to overcome antigen heterogeneity, to mitigate T-cell exhaustion and to prevent suppression by the tumor microenvironment; and
- Regional infusion of CAR-T cells for direct effect.

In particular, innovative CAR design and logic-gated approaches allow for exploiting the full therapeutic potential of CAR-T cells and enabling treatment of a broader range of cancer patients in the near future. Apart from autologous T-cells as the major source used at present, allogeneic cells including stem cell-derived, "off-the-shelf" T-cells may play an important role in the future.

In addition, genome-editing technology is being explored as a

strategy to advance the scientific engineering of the CAR. Compared with conventional CAR-T cells, CRISPR/Cas9-edited CAR-T cells have shown an enhanced potency, delayed differentiation and exhaustion – all findings that highlight genome-editing technology as a promising approach for additional changes and improvements to the infused CAR-T cells. In addition to genome-editing technology, other therapeutic measures—including chemotherapies, radiation, immune checkpoint blockade antibodies and cytokine treatment—also may be combined with CAR-T cell therapy to broaden the application and enhance the efficacy for individual cancer elimination. Despite progress in managing severe cytokine release and neurotoxicity, the mechanisms at hand are poorly understood. On that, drug developers and the global medical community agree that further research in CAR-T cell therapy for treating solid cancers deserves significantly more attention.

EFFICIENT MANAGEMENT OF LOGISTICS IN THE CLINIC

Managing patients and sample procurement during the critical "vein-to-vein" time in studies for autologous CAR-T therapies is complex and challenging. In addition to these studies having patients who are significantly ill, the processes in place require multiple parties and many handoff processes for study samples. Logistics in CAR-T studies require keen oversight, management of complex processes and an understanding of patient profiles and pathways. This is a true multidisciplinary approach in which leading academic teaching hospitals supporting this work are exploring more refined and innovative processes. Clinical research organizations (CROs) have a significant role to play here, not only in training, but also in oversight of the logistics process. There continues to be critical importance placed on comprehensive training at sites – a broader look beyond training for nurses, physicians and pharmacists. We are seeing an increasing need to engage and train administrative staff who are responsible for moving patients from one department/facility/site to another.

For example, CROs deploy clinical logistics coordinators who work closely with sites and sponsors to oversee and track patients and their samples—a closed loop approach to prescreening and slot allocation to apheresis through manufacturing and back to the patient for infusion.

Advances in development of "off-the-shelf" allogeneic products will help reduce manufacturing and thus logistical challenges. Furthermore, they also may provide a more functional, potent product for malignancies such as CLL, where T-cell dysfunction is common and frequently cannot be fully reversed during the manufacturing process.

REGULATORY AND HEALTH TECHNOLOGY ASSESSMENTS (HTA) STRATEGIES

As use cases for CAR-T increase, there are open requests from both regulators like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and organizations such as the National Institute for Health (NIH) and Care Excellence and Institute for Clinical and Economic Review for manufacturers to engage early on assessment and acceptance requirements for advanced therapies. These organizations are experiencing a steep learning curve as they address this initial wave of advanced therapies that have transformative or even curative potential.

Given the novelty and complexity of CAR-T and other cell and gene therapies, including the need to demonstrate transformative and longer-term effect, it is critical to plan for regulatory and market access requirements early in development. Many of these therapies have been launched with single-arm results and all of them require a registry. Optimizing the evidence synergies between pivotal trial design, real-world evidence and the registry is critical to ensuring acceptance and uptake for these therapies. This includes utilizing solutions like synthetic control arms to address the need for comparative evidence and how a registry can be a tool to support risk sharing and novel payment strategies in some markets.

Understanding regulatory and HTA/payer requirements early, planning for changing evidence development approaches for transformative therapies and approaching development in an integrated fashion are key ingredients to an efficient and comprehensive strategy for success. This is underscored by the uptick in emphasis on integrated scientific advice that we are seeing in the marketplace.

IMPACT OF COVID-19

The COVID-19 pandemic has caused significant constraints globally in the delivery of cellular therapy in order to ensure patient and site safety. This includes partial closures of outpatient clinics, decreased infusion suite capacity and a resultant decrease in clinical staff. It is acknowledged that CAR-T cell therapy requires intensive and valuable resources necessitating significant logistical planning.

In preparation for this surge of virally infected patients, hospitals across the world have instituted measures to defer multiple patient care interventions, including such treatments as autologous stem cell transplantation. Given that CAR-T cells are potentially curative for patients with an otherwise dismal prognosis, outpatient CAR-T administration should be considered, when feasible, to reduce inpatient health care utilization. This may not be practical to uniformly institute in all centers and must address available resources and the viral burden in the surrounding community. Consequently, inpatient admission may be more appropriate at certain centers.

LOOKING BEYOND 2020

Cell and gene therapeutics such as CAR-T have shifted the paradigm of care from palliative to potentially curative. Throughout 2020 and alongside global colleagues, we will continue to work with partners to explore increased sophistication and scientific engineering of the CAR, improve logistics throughout the life cycle of development, and keep patient experiences and needs at the forefront of global work to deliver life-changing therapeutics to those who need them most. **CP**

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