Changing gears to deliver CAR-T in your hospital

Enabling operational readiness for CAR-T therapy delivery in a hospital

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Content

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Executive summary

New advanced therapies, such as chimeric antigen receptor T-cell (CAR-T), are remarkable treatments for patients who have exhausted all other therapy options. These innovative therapies are delivered through non-traditional models and involve lengthy, complex, highly coordinated sets of activities within the healthcare provider's facilities. For providers, these therapies offer a number of opportunities, from improving their stature as leading-edge institutions to offering high-revenue-generating services. However, if not thoughtfully considered and appropriately planned, delivering these new advanced therapies presents tremendous financial and operational risks. This report sets out the strategic and readiness evaluation framework providers need to evaluate CAR-T therapy as a treatment to be offered.

1. Personalized medicine is here to stay

No therapeutic area highlights the potential benefits and promises of precision medicine better than oncology. While great strides have been made over past decades to treat cancer, the condition often becomes a "personalized disease" due to cellular adaption processes. Some cancers, initially responsive to generalized chemotherapies, develop resistance through unknown mechanisms and become unresponsive to treatments that were previously effective, resulting in relapse with limited treatment options

However, new technologies are enabling a shift away from treatment with potential for disease reoccurrence to treatments that can effect a cure. Furthermore, these technologies provide the basis for therapies tailored to the individual patient, with the advantage of eliminating the potential for diminishing treatment response. One such emerging technology is the immunotherapy approach called adoptive cell transfer (ACT). ACT involves collecting, modifying and using a patient's own immune cells to treat their cancer. While there are several types of ACTs, one that has demonstrated remarkable clinical success is chimeric antigen receptor (CAR) T-cell therapy.

CAR-T therapy is gaining momentum

CAR-T therapy uses genetically re-engineered versions of a patient's own T-cells to find cancer cells and defeat them throughout the body. These are, in every sense of the concept, personalized and precision therapies. The impressive clinical response to CAR-T therapy is driving explosive growth in uptake of the treatment. There are currently over 365 CAR-T therapies in various R&D stages in the US. Nearly 100 CAR-T therapies are in clinical development, many anticipated to enter the market within the next five to ten years[1]. It is, therefore, no surprise that the CAR-T therapy market is projected to grow at an annual rate in excess of 50 percent through to 2030. This market is expected to be valued at US$ 8.5 billion by 2028[2].

Developers have laid the foundation

Pharmaceutical manufacturers have led the development of CAR-T therapy, with marketing approval granted in the US, the EU and other major markets. This is not only having a great impact on patients, but also creating "new types" of opportunities within the healthcare network. These new types of opportunities arise from the unusual model of delivery of this therapy, as it requires very close collaboration between the manufacturer and healthcare provider throughout the treatment period. Traditionally, the sale of medication to a healthcare provider does not require much post-sales involvement from the manufacturer. However, this is not the case with CAR-T therapy, as the manufacturer plays a key role throughout the treatment journey. For example, one manufacturer offers to give a second treatment to a certain group of patients who do not respond to the first treatment and will not charge for the treatments if the desired outcome is not achieved. Consequently, this creates opportunities for providers to increase the value they offer, and to extend their services and reputations as innovators and centers of care.

CAR-T therapies are currently approved for use further down the treatment pathway, but with knowledge and experience increasing, it is foreseeable that this could change. This would create even more opportunities for the use of CAR-T in an increased number of patients.

1 https://www.marketwatch.com/press-release/car-t-therapies-market-2018-2030-2018-08-22
2 http://www.digitaljournal.com/pr/3227637#ixzz5gNlJvzBF

2. Providers are excited about CAR-T

Given the success of CAR-T therapy, there has been a lot of interest from healthcare providers in delivering this treatment. There are three main reasons why many healthcare providers are considering the opportunity that CAR-T therapy provides: remission, return, and renown.

Remission

As therapies go, CAR-T therapy has shown to be very effective in treating hematological cancers. Complete remission rates as high as 90 percent were seen in clinical trials for patients with relapsed and refractory B-cell acute lymphoblastic leukemia, and response rates greater than 50 percent have been seen in heavily pretreated chronic lymphocytic leukemia and non-Hodgkin lymphomas[3]. This is a major opportunity for healthcare providers, as these new therapies support what providers are very good at – delivery of improved health outcomes for patients.

More than 80 percent of children diagnosed with Acute Lymphoblastic Leukemia (ALL) can achieve long-term event-free survival (EFS) with existing treatments. However, for patients whose cancers return after chemotherapy or a stem cell transplant, there have been few or no treatment options.[i]

Novartis was the first company to generate impressive clinical data and subsequently launch its CAR-T therapy product, Kymriah, a one-time treatment for B-cell ALL. Clinical trial data demonstrated an 83 percent remission rate after three months in patients who had not responded to standard treatments.[ii]

i Tallen G. et al Journal of Clinical Oncology (May 2010)
ii Lymphomanewstoday.com (August 2017)

Return

Not all new therapies can support the delivery of improved health outcomes at an acceptable cost. According to published literature[4], there has been a trend of negligible incremental effectiveness, despite the rising cost per life year gained from recent cancer therapies. Research published and discussed at the 2018 annual meeting of the American Society of Hematology indicates that CAR-T therapy goes against the trend seen with recent hematology therapies, as it provides improvement in health outcomes (measured in quality-adjusted life years) to a degree higher than that from treatments for non-hematologic cancers and non-CAR-T treatments for hematologic cancers[5].

Renown

There are extended benefits for hospitals that develop the capability to provide CAR-T therapy to patients. They have the potential to attract clinicians who are keen to develop their competence with CAR-T therapy and would otherwise not have considered these hospitals as places to further their careers. In addition, existing talent in the hospital can develop competency for delivery of a cutting-edge medical intervention to patients. Furthermore, the opportunity to be a national or global research center of choice, and to publish research papers from firsthand clinical experience in an emerging treatment area, will make the hospital a desirable career destination for hematologists and oncologists.

3 https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.24238
4 J Econ Perspect 2015;29:1
5 https://ash.confex.com/ash/2018/webprogram/Paper116763.html

3. Due diligence should precede investment

The investment case has to be carefully considered

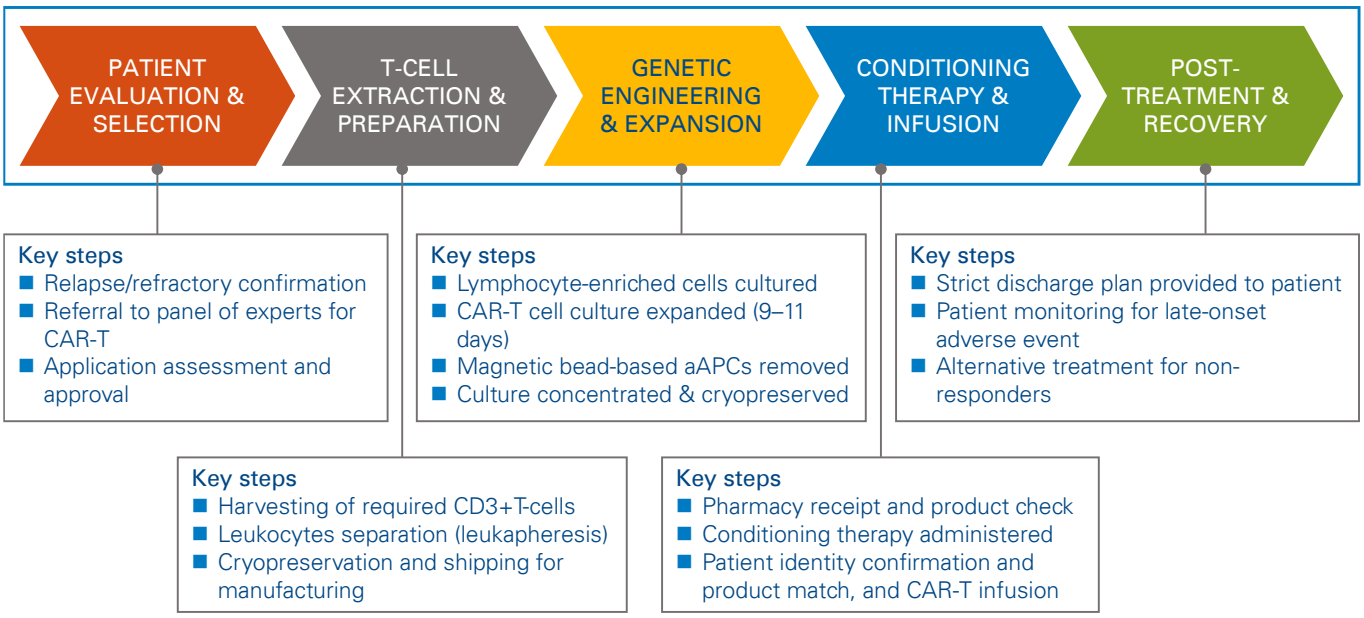
The decision to invest resources to support the delivery of ACT-based therapies requires careful evaluation by healthcare providers. Basic considerations such as whether there are sufficient numbers of patients to justify the investment have to be made. Not only are there significant upfront infrastructure costs, but an entirely new model of work is required to operationalize the delivery of treatments like CAR-T therapy. Examples include process and eligibility criteria to ensure that patients with the most need are selected, laboratories and facilities to collect and process the required cells, quality management systems, inventory systems, and care infrastructure to manage patients during cell processing and following infusion.

Establishing CAR-T and ACT-based services in a hospital generally begins with development of an initial high-level business case. As with any new therapy, business model parameters must be rigorously considered since specific data is still unavailable (or emerging). The business case will have to rely on many assumptions due to lack of information on the operational complexities of the service delivery. While the high-level business case is vital in the decision-making process, taking it on its own without further analysis of the detailed set-up requirements of a CAR-T service will be reckless. It is therefore imperative to understand in detail the operational requirements, gaps in a hospital's infrastructure, and what is needed to bridge the gap before finalizing the business case or building an implementation roadmap for CAR-T therapy.

Stay on the right path

One of the best ways to assess the operational readiness of a provider to introduce CAR-T therapy is to use the treatment pathway as a framework to understand the infrastructure needed to deliver the service. The treatment pathway is ideal because it is an integrated, end-to-end view that considers the needs of the patients, manufacturer, provider, and payer. It provides a comprehensive view – from the moment the patient is assessed for eligibility to the post-treatment phase. Applied robustly, the treatment pathway will highlight the major requirements and gaps within a provider's existing set-up, as well as provide vital information to strengthen the initial business case.

Figure 1: CAR-T treatment pathway



Source: Arthur D. Little

4. Follow the treatment pathway

From a high-level view, the CAR-T treatment pathway consists of five main steps:

Patient evaluation and selection

The first step spans the patient journey from the relapse/refractory phase of previous therapies through to selection and approval for CAR-T therapy. This includes the battery of tests required to confirm relapse and eligibility for CAR-T therapy, the application for approval sent to the governing panel (a local and/or national panel of cancer experts), and approval or authorization to proceed with the therapy. It also involves the provision of alternative treatments for patients who are not eligible or whose applications are unsuccessful.

T-cell extraction and preparation

The next step in the framework involves the necessary activities and procedures required to extract the required T-cells from a patient's blood – a process called leukapheresis. Ideally, leukapheresis is optimized to generate sufficient materials in one session. It involves collecting a sample of the patient's blood and extracting the lymphocytes, before returning the remaining blood to the patient's bloodstream. This step also involves labeling and cryopreservation of the sample, processing the required paperwork for transportation of the sample to the manufacturing center, and linking the hospital's system with the logistics system of the manufacturer in order to ensure electronic tracking of the order, processing, and delivery.

Genetic engineering and expansion

At this step, the harvested T-cells are genetically modified to express the chimeric antigen receptor, and subsequently expanded in vitro until enough CAR-T cells are manufactured for effective treatment. This process takes a few weeks and requires coordinated communication with the medical center treatment team, in order to ensure that the patient receives interim treatment or initiate any therapy washouts. Finally, the culture is then cryopreserved and returned to the treatment center. Currently, for approved treatments, the patient sample has to be sent off to contract manufacturers, who carry out genetic engineering and expansion. There are emerging approaches, currently in clinical trials, which may allow hospitals to do genetic engineering and expansion.

Lymphodepletion conditioning therapy

At this stage, the CAR-T cells are infused into the patient, who is then carefully monitored within the treatment facility. Prior to infusion, it is common for the patient to be given a dose of chemotherapy and other lymphodepletion conditioning therapy to maximize the therapeutic effect of the treatment. Strict quality control checks are also implemented to ensure that the right product is given to the right patient. Finally, reinfusion might also be required, depending on the success of the first CAR-T cell infusion.

Post-treatment and recovery

The final step of the CAR-T treatment journey involves assessment of the therapeutic and adverse effects of the therapy before the patient is discharged. The assessment includes monitoring the patient for toxicity effects of the therapy and, as appropriate, management of any side effects. This step also involves significant education of the patient and caregiver, particularly on possible late-onset adverse events. The patient often requires remote monitoring post-discharge and is expected to reside within a two-hour driving radius of the treatment center for a number of weeks. Finally, the treating hospital is required to provide post-therapy reports to the appropriate health authority.

5. Do a thorough gap assessment

Providers planning to add CAR-T therapy to their existing services will need to assess the gaps in the treatment pathways in their hospitals, using a gap assessment framework.

Governance and guidelines

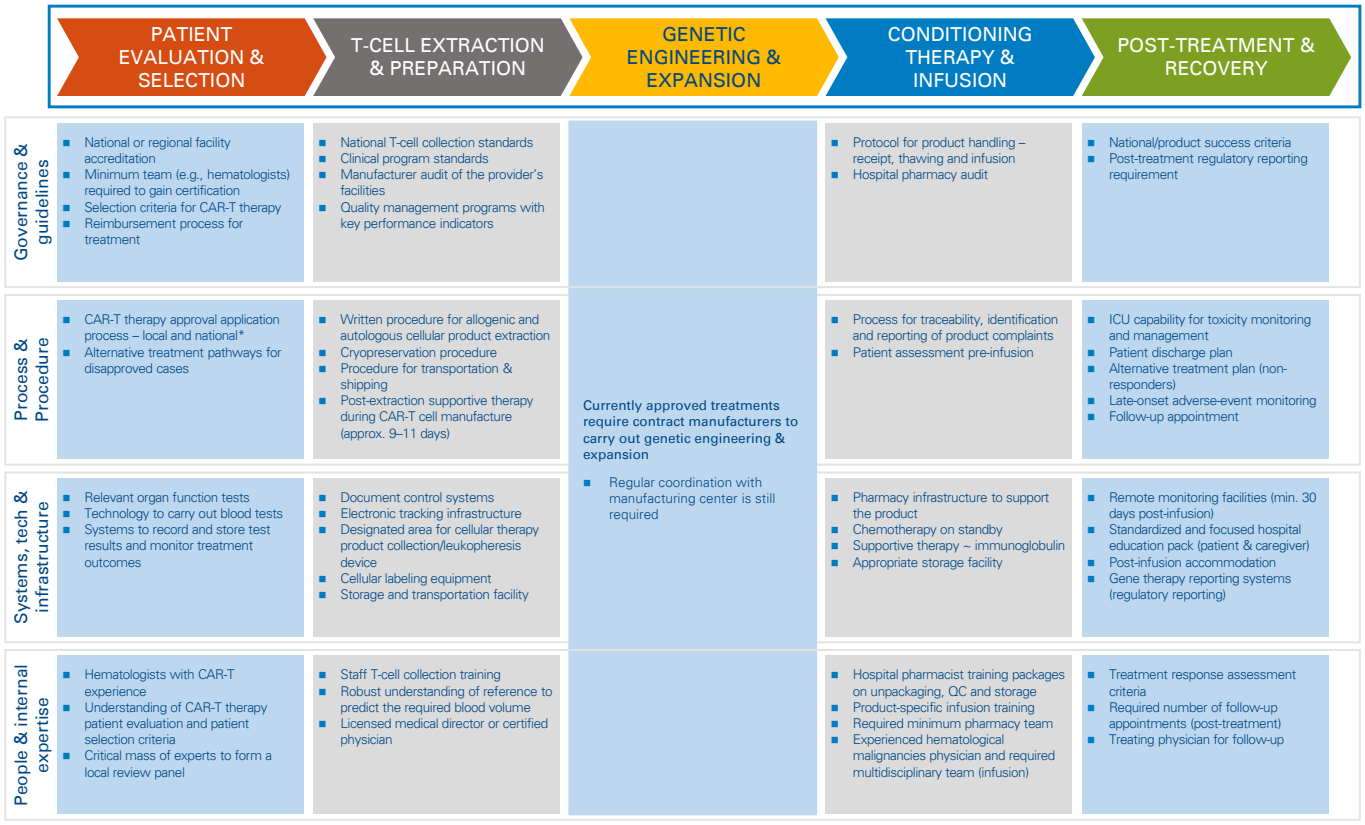
This involves obtaining the necessary accreditations and certifications from the governing bodies and manufacturers to provide this service. It also involves establishing the governance required to assess and approve individual CAR-T therapy request applications. It is be very important for providers to decide whether they want to be involved in product manufacturing as this will influence what is required from a governance perspective. Some providers might need to form new panels of experts or augment the scope of existing suitable panels to provide the required governance for their hospitals. In some countries, governance may extend beyond the local (hospital) level to a regional or national review panel.

CAR-T is an unconventional therapy, and as such, the guidelines for therapy (from T-cell extraction and labeling to genetic modification and reinfusion into the patient) may not exist. These guidelines, which could be local, national and/or product specific, will need to be established.

Processes and procedures

Assessing the internal processes required to deliver CAR-T therapy could reveal gaps such as lack of a therapy application process or the absence of a process for labeling and storage of the culture. Upholding the high-quality and process standards for this therapy requires either creation of new processes or strengthening of existing processes. These are also subject to GxP audits. Medical procedures specific to CAR-T therapy may also be an area with gaps. An example could be absence of processes for the supportive therapy that must be administered during the weeks of CAR-T cell manufacture.

Figure 2: CAR-T treatment pathway-based gap assessment framework



Source: Arthur D. Little
Note: * Where applicable

Systems and infrastructure

Additional control systems could be required to supplement the manual effort involved in the therapy delivery process and minimize human errors – which could be very costly with this therapy. Examples include robust data and document control systems, overarching quality management systems and cellular labeling equipment, and pharmacy controls and checks.

This category also includes facilities (e.g., appropriate designated areas for collection and storage of cellular therapy products) needed to smoothly run the operation and ensure patient safety and effective therapy. A gap assessment here involves review of the infrastructure required to link the hospital's system with the logistics systems of the manufacturer so ordering, processing, and delivery can be tracked and completed electronically.

People and internal expertise

As with introduction of any new advanced therapy, additional expertise will be required to enable successful implementation. This includes upskilling of existing staff members (e.g., hospital pharmacist training packages on unpackaging, QC and storage of CAR-T culture) and the associated changes to their job descriptions. In most cases, additional external personnel will be needed to provide expertise that is not available within the hospital (e.g., a product-certified physician) to cover the additional work demand. Assessing the necessary end-to-end expertise and comparing it to the current internal proficiency will highlight strengths and significant shortfalls.

6. Change gears with CAR-T therapy

CAR-T therapy is an exciting development to add to a healthcare provider's arsenal and give hope to patients who would otherwise be left with no real alternatives. However, hospitals will have to move quickly if there is real interest in developing the capability to deliver it. This is because the number of patients that will qualify for CAR-T therapy is so low that it will not make investment sense to develop the capability if another provider in the geographical region is already providing the service. For the foreseeable future, while the technology will still be expensive, CAR-T therapy will only be delivered by hospitals that are motivated to quickly establish themselves as the providers of the service in their regions. That journey begins by developing a high-level business case and using the treatment pathway framework to assess operational readiness and uncover the delivery gaps. This can assist in developing a more detailed business case. Once the investment picture is clear and the returns are considered compelling, it will be time to change gears and begin the journey to establish your hospital in a higher league of healthcare providers.

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Changing gears to deliver CAR-T in your hospital

CAR-T is an exciting treatment option with benefits to patients. It can also enhance the status of hospitals that provide it. The provision of CAR-T requires careful consideration before embarking on a journey to develop the needed capabilities. The CAR-T gap assessment framework helps to uncover the operational adjustments that interested hospitals must make. This will support the development of a robust business case to inform the investment decision.

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