Arthur D Little

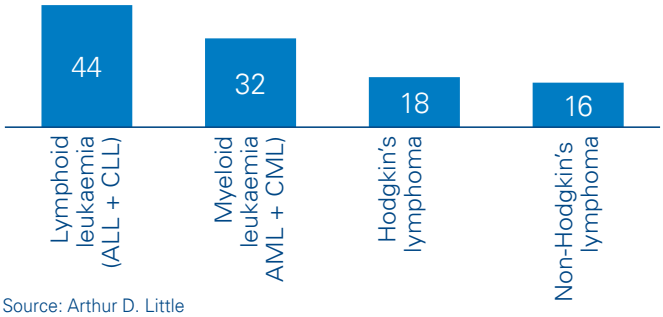
Viewpoint

CAR-T on site: Forgoing the extra mile

Adopting on-site manufacturing of CAR-T cells in your hospital to improve patient outcomes

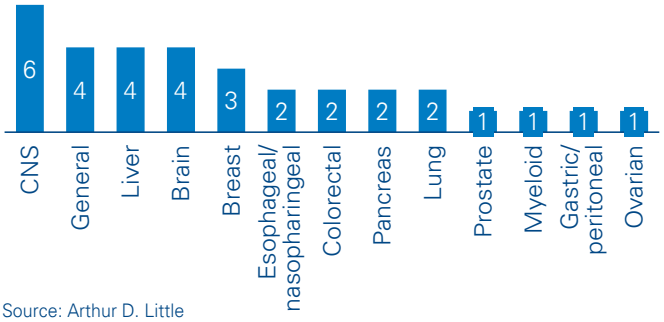
CAR-T (chimeric antigen receptor T-cell) therapy involves the use of genetically re-engineered versions of a patient's own T-cells to find cancer cells and defeat them. As of March 2020, there are two CAR-T therapies licensed for use – Kymriah®[1] and Yescarta®[2]. CAR-T has pushed the boundaries of medicine, and the success observed in patient treatment has created interest in the use of CAR-T to treat a number of other types of tumors. This is evidenced by the number of clinical trials involving the use of CAR-T to treat a range of cancers (Figures below)[3]. Existing treatments require CAR-T cells to be manufactured remotely and transported to treatment centres for administration. Emerging technology now provides the possibility for CAR-T cells to be manufactured on site. In this viewpoint we outline the advantages of on-site CAR-T manufacturing

Clinical trials involving the use of CAR-T therapy to treat hematological malignancies



Source: Arthur D. Little

Clinical trials involving the use of CAR-T therapy to treat solid tumors



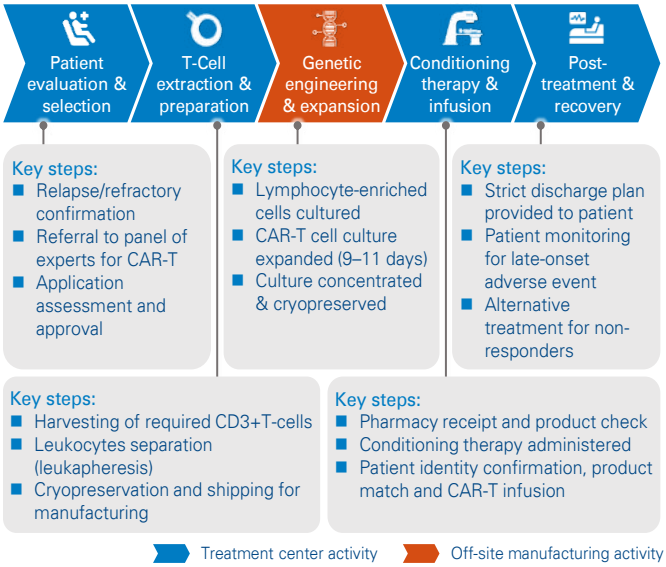
Source: Arthur D. Little

Existing approved treatments are based on off-site manufacturing

In a previous paper titled "Changing gears to deliver CAR-T in your hospital," we outlined the treatment pathway for approved CAR-T therapies. With the current approved CAR-T treatments, the patient is evaluated and selected for treatment. Then their T-cells are extracted, leukocytes are separated, and the sample is transported to an off-site manufacturing facility, where the genetic engineering and cell expansion takes place. The final product is returned to the treatment facility for infusion into the patient, who would have received some coordinated conditioning therapy in preparation for the treatment. After treatment administration, the post-treatment plan is implemented to support the patient's recovery. The logistical impact of off-site manufacturing is that the patient has to wait for an extended period of time for the cells to be processed and returned to the hospital before the treatment can continue. There are logistical risks associated with the transportation of samples, e.g., delayed arrivals, lost samples and sample deterioration. CAR-T therapy can be enhanced if the "extra mile" is eliminated without any impact on the quality of treatment.

1 https://www.novartis.us/news/media-releases/ Accessed February 2020
2 https://www.gilead.com/news-and-press/press-room/press-releases/ Accessed February 2020
3 Adapted from Zhao L, Cao YJ. Engineered T Cell Therapy for Cancer in the Clinic. Front Immunol. 2019;10:2250. Published 2019 Oct 11.

Treatment pathway for CAR-T therapy



Source: Arthur D. Little analysis

On-site CAR-T production is gaining momentum

As technology continues to evolve and more research is done with CAR-T, published papers[4,5,6,7] that explore the possibility of carrying out every step of the CAR-T treatment pathway at the hospital have begun to emerge. The idea of this innovative move is to take advantage of the benefits of on-site manufacturing and improve patient treatment. It may present an opportunity for hospitals to offer an advanced and innovative treatment to patients. It also gives hospitals an opportunity to do clinical research in an area of cutting-edge medicine.

On-site production of CAR-T cells can deliver a number of potential advantages:

1. Speed of availability – on-site production may be able to speed up the "vein to vein" time of patient treatment. One published study suggested that on-site-produced CAR-T could assist certain patients, who would otherwise not benefit from off-site manufactured CAR-T due to the rapid progression of their diseases.[6]
2. Wider access to treatment – on-site production may provide an opportunity for clinicians to consider CAR-T in a different light and enable wider access to this innovative treatment. This is because the availability of on-site manufacturing increases the independence of delivery by hospitals. This can be a game changer in countries that restrict movement of genetic materials and patient samples beyond their borders and do not have their own CAR-T manufacturing facilities.
3. Ease of handling and improved cell viability[8] – on-site production requires less process steps because some steps associated with off-site manufacturing, such as transportation and post-transportation thawing, will not be necessary. This will serve as an advantage for treatment. In a phase 3 trial that failed to meet its clinical end point, a review of the study suggested that thawing the cryopreserved cells may have contributed to the failure of the clinical trial. Another study suggested that the viability of the cells could have been compromised by vibrations during transportation.

The advantages of on-site manufacturing of CAR-T cells could increase its attractiveness to hospitals that may have considered CAR-T in the past but chose not to offer the treatment to patients for various logistical reasons. However, bringing the production of CAR-T in-house may present a number of extra responsibilities for hospitals and require effort (and even costs) that treatment using off-site-manufactured CAR-T cells does not.

Evaluation is the first step in considering on-site-produced CAR-T therapy for your hospital

When considering on-site CAR-T therapy as a treatment to be delivered, it is prudent to first prepare an initial or outline business case to assess the opportunity. Subsequently, an operational readiness assessment of the hospital or treatment center may be necessary as part of a more detailed business case.

In carrying out an operational-readiness assessment, it is important to consider four key domains at each step of the treatment journey:

Governance and guidelines

This refers to the necessary accreditations, certifications and guidelines from the governing bodies and developers of the on-site manufacturing technology. It also involves establishing the governance required to assess and approve individual CAR-T therapy request applications. Some hospitals may have to form new panels of experts or augment the scope of existing suitable panels to provide the required governance. In some countries, governance may extend beyond local hospitals to regional or national review panels.

4 Caimi PF et al. Phase 1 Study of on Site Manufactured Anti-CD19 CAR-T Cells: Responses in Subjects with Rapidly Progressive Refractory Lymphoma. Blood (2019) 134 (Supplement_1): 4074.
5 Zhu F et al. Automated manufacturing of CD20.19 bi-chimeric antigen receptor T (CAR-T) cells at an academic centre for a phase 1 clinical trial in relapsed, refractory NHL. Abstracts /Biol BloodMarrow Transplant 25(2019) S70-S75
6 Caimi PF et al. On Site Manufacture of AntiCD19 CAR-T Cells. Responses in Subjects with Rapidly Progressive Refractory Lymphomas. Biology of Blood and Marrow Transplantation Volume 26, Issue 3, Supplement, March 2020, Pages S234-S235
7 Kebriaei P et al. Phase I trials using Sleeping Beauty to generate CD19-specific CAR T cells. J Clin Invest. 2016;126(9):3363-3376
8 Karen Coopman and Nick Medcalf. From production to patient: challenges and approaches for delivering cell therapies. Stem Book Cambridge (MA): Harvard Stem Cell Institute; 2008-.ISSN: 1940-342

Processes and procedures

Processes are required to outline how different treatment-related activities should be carried out to ensure consistency and maintenance of high-quality standards. These include processes and procedures for selecting patients, handling extracted cells, testing and release of on-site manufactured CAR-T cells, managing post treatment side effects etc. These processes should be robust and subject to relevant GxP audits.

Technology and infrastructure

Technology and infrastructure play a central role in the delivery of CAR-T on site. They are needed to carry out the activities that precede genetic engineering and expansion of T-cells. These activities include running blood tests and harvesting the patient's T cells. Technology and infrastructure are also required to manage the patient after they have been infused with the CAR-T cells. However, the most cutting-edge technology and infrastructure on the treatment pathway involve the set-up to produce the CAR-T cells on-site. The technology for this key step is available, with a number of clinical trials having been published in the last few years[7,6]. Setting up the technology and infrastructure for on-site CAR-T cell manufacture will require close collaboration with the developer company to support full implementation and compliance of on-site CAR-T cell manufacture.

Miltenyi Biotech has developed an automated manufacturing process for lentiviral gene modification and expansion of selected T-cells. The CliniMACS Prodigy® TCT (T-Cell Transduction) Process software allows purification and polyclonal T-cell stimulation, followed by gene modification and expansion of T-cells in a single-use closed-tubing set. Published studies suggest that the TCT process can handle highly diverse cell sources while yielding a consistent cellular product.

People and internal expertise

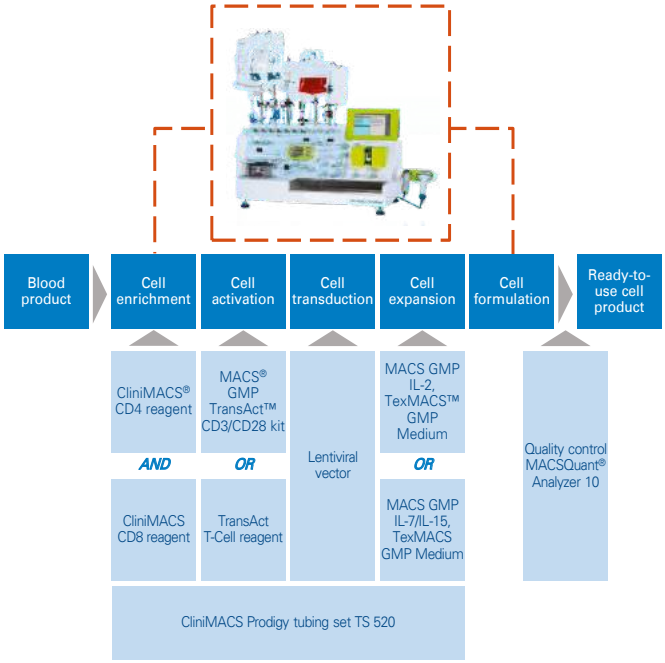
As with introduction of any new advanced therapy, additional expertise will be required to enable successful on-site manufacture and delivery of CAR-T therapy. As well as upskilling of existing staff, external personnel will be needed to provide expertise that is not already available within the hospital. On-site-manufactured CAR-T cells will require strategic, technical and project management expertise to get the treatment center ready to deliver the treatment.

On-site CAR-T treatment pathway and readiness assessment framework

	Patient evaluation & selection	T-cell extraction & preparation	Genetic engineering & expansion	Conditioning therapy & infusion	Post-treatment & recovery
Governance & guidelines	■ National or regional facility accreditation ■ Minimum team (e.g., hematologists) required to gain certification ■ Selection criteria for CAR-T therapy ■ Reimbursement process for treatment	■ National T-cell collection standards ■ Clinical program standards ■ Manufacturer audit of the provider's facilities ■ Quality management programs with key performance indicators	■ National approval of vector safety and efficacy data ■ National guidelines for on-site manufacturing, e.g., cleanroom standards for CAR-T manufacturing ■ Developer guidelines for operation of the CAR-T production system	■ Protocol for product handling ■ Protocol for patient conditioning	■ National/product success criteria ■ Post-treatment regulatory reporting requirement
Process & procedure	■ CAR-T therapy approval application process – local and national* ■ Alternative treatment pathways for disapproved cases	■ Written procedure for cellular product extraction ■ Post-extraction supportive therapy during CAR-T cell manufacture	■ Manufacturer's step-by-step guide for on-site production of CAR-T cells. ■ Hospital process document for handling, storage and on-site manufacture of CAR-T cells ■ Product-testing and release criteria	■ Process for traceability, identification and reporting of product complaints ■ Patient assessment pre-infusion	■ ICU's capability for toxicity monitoring and management ■ Patient discharge plan ■ Alternative treatment plan (non-responders) ■ Late-onset adverse-event monitoring ■ Follow-up appointment
Systems, tech & infrastructure	■ Relevant organ-function tests ■ Technology to carry out blood tests ■ Systems to record and store test results and monitor treatment outcomes	■ Document-control systems ■ Designated area for cellular therapy product collection/leukapheresis device ■ Cellular labelling equipment ■ Storage facility	■ Cleanroom (if required) for CAR-T cell manufacture ■ Storage facility for genetically engineered cells ■ Closed-system CAR-T cell manufacturing equipment	■ Pharmacy infrastructure to store the product ■ Chemotherapy on standby ■ Supportive therapy (immunoglobulin) ■ Appropriate storage facility	■ Remote-monitoring facilities (min. 30 days post-infusion) ■ Standardized and focused hospital education pack (patient & caregiver) ■ Post-infusion accommodation ■ Gene-therapy reporting systems (regulatory reporting)
People & internal expertise	■ Hematologists with CAR-T experience ■ Understanding of CAR-T therapy patient evaluation and patient selection criteria ■ Critical mass of experts to form a local review panel	■ Staff T-cell collection training ■ Robust understanding of reference to predict the required blood volume ■ Licensed medical director or certified physician	■ Trained technologists to operate the CAR-T cell manufacturing system ■ Training on product testing and release	■ Hospital pharmacist training on QC and storage ■ Product-specific infusion training ■ Required minimum pharmacy team ■ Experienced hematological malignancies physician and required multidisciplinary team	■ Understanding of treatment-response assessment criteria ■ Required number of follow-up appointments (post-treatment) ■ Treating physician for follow-up

Source: Arthur D. Little

Process for on-site CAR-T cell production using the CliniMACS Prodigy technology



Source: Arthur D. Little

Get started with an evaluation for on-site CAR-T delivery in your hospital

CAR-T, a game-changing treatment, is available now but constantly evolving. More and more patients will request CAR-T therapy as it gains approval to treat more diseases. To be on the front foot, forward-thinking hospitals interested in CAR-T therapy should begin to examine the possibility of delivering it on site for the advantages this brings. It is a great time to consider delivering on-site CAR-T therapy because the data needed for marketing authorization are yet to be produced, hence, all the necessary preparations can be made in advance of a license being granted. If you want to deliver CAR-T therapy without the extra mile, you must begin an evaluation of on-site production of CAR-T for your hospital without delay.

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