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Would you, could you drive CARs to point-of-care manufacturing? Yes, you should!

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Approximately 45,070 patients worldwide have received chimeric antigen receptor T-cell (CAR T) therapy for hematological malignancies since regulatory approval of the first CAR T products in 2017.[1] However, the demand for these transformative therapies is significantly higher as the 2025 newly diagnosed cases of non-Hodgkin lymphoma and multiple myeloma in the United States are expected to be 80,350 and 36,110 respectively.[2] This supply/demand imbalance is a challenge that will grow as new CAR T therapies are approved for other indications such as solid tumors, autoimmunity, and infection.

There are seven commercially available CAR T products, and each is produced at centralized contract manufacturing organizations (CMOs) located throughout the United States. The ability to deliver adequate supply is limited by the small numbers of certified manufacturing centers, production slots, and trained staff. The manufacturing process is complex, lengthy – typically 3-6 weeks, and expensive due to intricate coordination of both material supply and product distribution. Consequently, the per dose prices of CAR T are exorbitant, ranging from $375,000 to $640,000.[3] CAR T therapy can cost as much as $1 million or more per patient after adding charges for inpatient stay, toxicity management, and outpatient follow-up.[4]

This combination negatively impacts accessibility to and efficacy of treatment with CAR T. Indeed, long wait times for delivery of CAR T are associated with increased mortality as seen in multiple myeloma where as many as 1 in 4 patients die while waiting to receive their CAR T.[5] For patients who do receive CAR T, the delayed treatment often means patients are receiving CAR T later in their disease course which often diminishes treatment effectiveness and increases toxicities.[6]

Application of a decentralized point-of-care (POC) manufacturing model addresses some of the accessibility issues. POC is usually academic or hospital-based and mostly used to prepare investigational CAR T. This model removes the expense of and time to ship materials and products to and from a CMO and typically reduces the wait time for an open manufacturing slot to less than two weeks. This results in a 2- to 3-fold reduction in total patient wait time as compared to commercial CAR T.[7] The starting material, patient leukapheresis, for the POC process is frequently collected within 48 hours of the start of manufacturing and used fresh not cryopreserved as is necessary for centralized manufacturing. Similarly, the final CAR T product is frequently infused as a fresh cell formulation rather than cryopreserved for shipping from the CMO to the treatment site. Foregoing cryopreservation saves both time and money and may improve T-cell fitness.

Implementation of automated closed-system manufacturing platforms at POC can further ameliorate the financial toxicity of commercial CAR T. These platforms streamline and standardize the manufacturing process and reduce manual labor, thus cutting the production cost of CAR T to an estimated $78,849 in 2019.[8] Moreover, automated systems accelerate the process such that the time to final CAR T product is 8 to 14 days.[7] This makes POC CAR T an attractive option to support patients who cannot wait 3-6 weeks for the treatment due to rapidly progressing disease.

POC manufacturing is practicable, but it requires a substantial financial commitment to (1) build, validate, and maintain a controlled environment manufacturing space, (2) purchase and validate manufacturing and analytical quality control equipment, (3) recruit and train skilled personnel, and (4) provide quality management oversight. At our institution, the cost to convert and equip a 1,450 square foot space into a cleanroom suite with four ISO7 and two ISO8 rooms was nearly $1.5 million dollars in 2018. Demonstrated efficacy of POC therapies could be helpful to justify the high cost of cleanroom installation.

In this issue of *Haematologica*, Marcus and colleagues from Chaim Sheba Medical Center (Israel), Memorial Sloan Kettering Cancer Center (MSKCC, US), and Rambam Health Care Campus (Israel) directly compare treatment outcomes after patients received CD19-directed CAR T made locally at Sheba Medical Center or commercially prepared axi-cel and tisa-cel.[9] A total of 330 patients were included in the analysis consisting of 94 who were treated at Sheba with locally produced CAR T versus 132 and 104 in the axi-cel and tisa-cel treated groups, respectively. The number of patients in each cohort is robust and provides meaningful comparisons. Propensity score analysis was used to balance the characteristics of subjects in the commercial versus local manufactured groups thereby reducing systematic error.

Sheba Medical Center achieved a CAR T manufacturing success rate of 98.8%, which is higher than the rates reported for axi-cel (96%) and tisa-cel (91%).[10,11] Patients treated with locally manufactured CAR T were younger and had a higher frequency of elevated lactate dehydrogenase, primary refractory disease, and higher tumor burden. Even so, non-relapse mortality, overall survival, and progression-free survival in the POC cohort were similar to those of commercial CAR T. The vein-to-vein time for POC CAR T of 11 days was significantly shorter than the delivery times for axi-cel or tisa-cel of 38 or 44 days. This is consistent with the use of POC manufacturing for patients who needed more urgent treatment.

These findings affirm the value of having both central and decentralized options for manufacturing CAR T where an option is selected based on the patient's disease characteristics. This report is an important contribution and timely given the need to increase accessibility to CAR T therapy and the ongoing need for POC manufacturing of investigational immune cell therapies. In addition, POC manufacturing as described in this paper could allow access to CAR T for patients who lack suitable insurance coverage or who need charity care. Advanced cellular therapeutics are here to stay and it is incumbent on its practitioners to find ways to deliver it more efficiently and cheaply. This paper offers a safe and effective pathway forward.

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