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Short Communication

A hub-and-spoke model to deliver effective access to chimeric antigen receptor T-cell therapy in a public health network: the Catalan Blood and Tissue Bank experience

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ABSTRACT

Background aims: To describe and analyze whether a hub-and-spoke organizational model could efficiently provide access to chimeric antigen receptor (CAR) T-cell therapy within a network of academic hospitals and address the growing demands of this complex and specialized activity.
Methods: The authors performed a retrospective evaluation of activity within the Catalan Blood and Tissue Bank network, which was established for hematopoietic stem cell transplantation to serve six CAR T-cell programs in academic hospitals of the Catalan Health Service. Procedures at six hospitals were followed from 2016 to 2021. Collection shipments of starting materials, CAR T-cell returns for storage and infusions for either clinical trials or commercial use were evaluated.
Results: A total of 348 leukocytapheresis procedures were performed, 39% of which were delivered fresh and 61% of which were cryopreserved. The network was linked to seven advanced therapy medicinal product manufacturers. After production, 313 CAR T-cell products were shipped back to the central cryogenic medicine warehouse located in the hub. Of the units received, 90% were eventually administered to patients. A total of 281 patients were treated during this period, 45% in clinical trials and the rest with commercially available CAR T-cell therapies.
Conclusions: A hub-and-spoke organizational model based on an existing hematopoietic stem cell transplantation program is efficient in incorporating CAR T-cell therapy into a public health hospital network. Rapid access and support of growing activity enabled 281 patients to receive CAR T cells during the study period.

Introduction

In recent years, advanced therapy medicinal products (ATMPs) have revolutionized biomedicine with new approaches to fighting life-threatening diseases. In particular, chimeric antigen receptor (CAR) T cells stand out as a revolutionary type of immunotherapy in which engineered T lymphocytes directed toward specific cancer antigens recognize and eliminate tumor cells [1]. More than 500 CAR T-cell clinical trials for the treatment of different cancer types are currently being conducted worldwide (as registered at ClinicalTrials.gov fourth quarter of 2021). The first two autologous CAR T-cell therapies, tisagenlecleucel (Kymriah, Novartis; Yescarta, Gilead) and axicabtagene ciloleucel (Yescarta), were authorized for the treatment of specific B-cell malignancies by the United States Food and Drug Administration in 2017 and 2018 [2,3], respectively, and by the European Commission in 2018 [4,5]. Since then, three additional therapies have been approved: brexucabtagene autoleucel (Tecartus) and lisocabtagene maraleucel (Breyanzi) to treat B-cell malignancies and idecabtagene vicleucel (Abecma) to treat multiple myeloma [6–11].

Incorporating CAR T-cell therapy into the health care system entails complex and highly specialized procedures and poses major logistics and supply chain challenges. It is therefore essential to establish the appropriate infrastructure for managing CAR T-cell products to meet the complex medical, logistics, training, quality and regulatory requirements. This is especially important when one of the main participants in this process is academic hospitals, which, although working under strict health care procedures, are usually far from the stringent and well-established standards of the pharmaceutical industry. Additionally, CAR T-cell products are subject to

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regulations specific to medicinal products for human use [12–14] and consequently fall under the responsibility of the hospital pharmacist, who, in turn, might not have cell processing experience and the required special infrastructure in place.

In this regard, as CAR T-cell practices share many similarities with the well-established hematopoietic stem cell transplantation (HSCT) process in the clinical setting, the use of an already established workflow could facilitate their implementation. Both procedures start with cell collection by leukocytapheresis. The CAR T-cell starting material is then delivered fresh or cryopreserved to the ATMP manufacturer. After production, the CAR T-cell product is shipped back to the hospital for storage and infusion using the same workflow and infrastructure as the HSCT program. For this reason, many cell therapy processing laboratories (CTPLs) have added externally manufactured investigational or commercially available CAR T-cell therapies to their HSCT workflow [15].

In November 2018, the Spanish Ministry of Health approved the *Management Plan for Advanced Therapies in the National Health System: CAR T-Cell Medicinal Products* [16]. The plan established an organizational and health care model to achieve planned, fair, efficient and safe access to the use of ATMPs. Among other things, it defined a set of criteria for designating centers to treat patients with CAR T-cell therapy within the Spanish National Health System. Center selection criteria were based on clinical experience (including activity in apheresis and cell processing), quality certification (Joint Accreditation Committee of the International Society for Cell & Gene Therapy and European Society for Blood and Marrow Transplantation [JACIE]), coordination between professionals, clinical experience with CAR T-cell therapies and Good Manufacturing Practice ATMP manufacturing capabilities. The authors' aim was to describe how the CTPL of the Catalan Blood and Tissue Bank (Barcelona, Spain) has accommodated the increasing demand for activities related to CAR T-cell therapy and how its hub-and-spoke organizational model has facilitated the designation of six affiliated public hospitals to treat patients with CAR T-cell therapy according to the Spanish management plan.

Catalan Blood and Tissue Bank Hub-and-Spoke Organizational Model

The Catalan Blood and Tissue Bank is a public agency of the Catalan Ministry of Health whose mission is to guarantee the supply and proper use of human blood in Catalonia (7.5 million inhabitants). In order to ensure consistent safety and quality in all procedures, the Catalan Blood and Tissue Bank established a hub-and-spoke model to deliver transfusion services to the hospital network. Thus, one core processing center/laboratory (hub) centralizes blood component preparation activities and quality control testing (immunohematology and HLA testing) and connects to a network of nine Catalan Blood and Tissue Bank hospital units located in referral hospitals (spokes) that collect blood donations and receive and provide blood components for transfusion (Figure 1) [17].

Based on this model, cell therapies for HSCT have been progressively incorporated into the working practices of the Catalan Blood and Tissue Bank since 2001. Similarly, one single CTPL located at Catalan Blood and Tissue Bank (CBTB) headquarters (hub) is connected to nine collection/delivery centers (CBTB hospital units/spokes) located within the hospitals. The CBTB is a single tissue establishment (license no. ES000049) that provides services. The Catalan Blood and Tissue Bank provides services to 11 transplant centers with 11 autologous and five allogeneic transplant programs. This integrated structure holds joint JACIE accreditation, allowing cell collection and processing to support more than 500 HSCTs per year.

Using this organizational model, the Catalan Blood and Tissue Bank started to support CAR T-cell activities in these hospitals when clinical trials began in 2016. In April 2019, the Spanish Ministry of Health designated 10 centers to treat adult patients (eight nominal

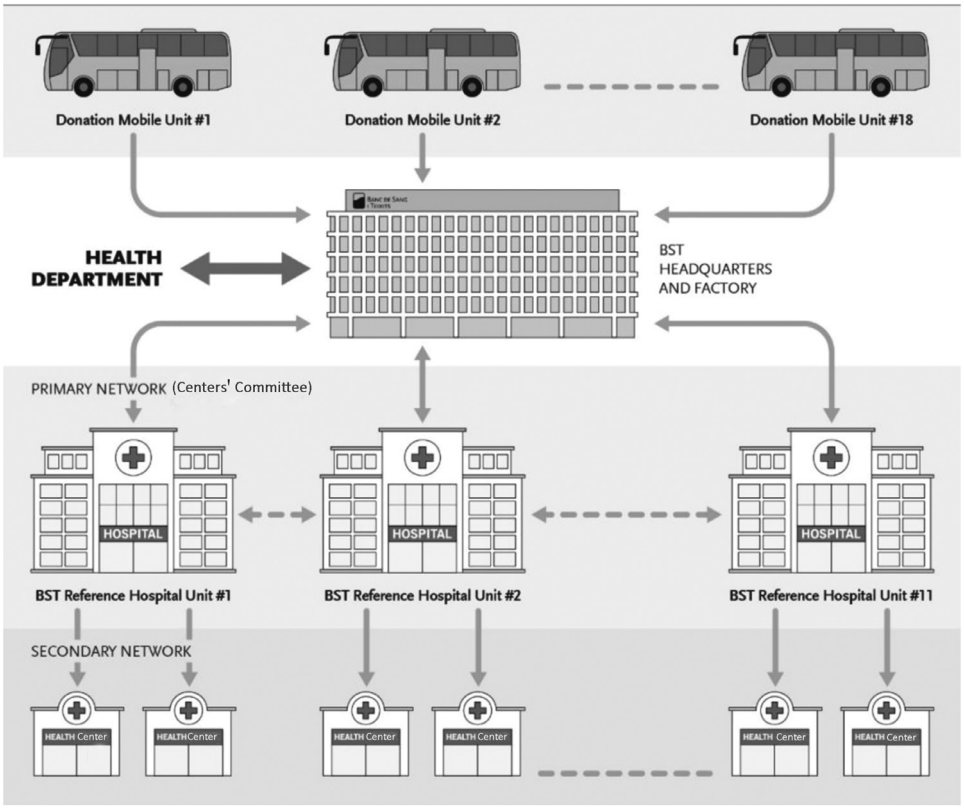

Fig. 1. Hub-and-spoke model of the Catalan Blood and Tissue Bank. BST, Banc de Sang i Teixits.

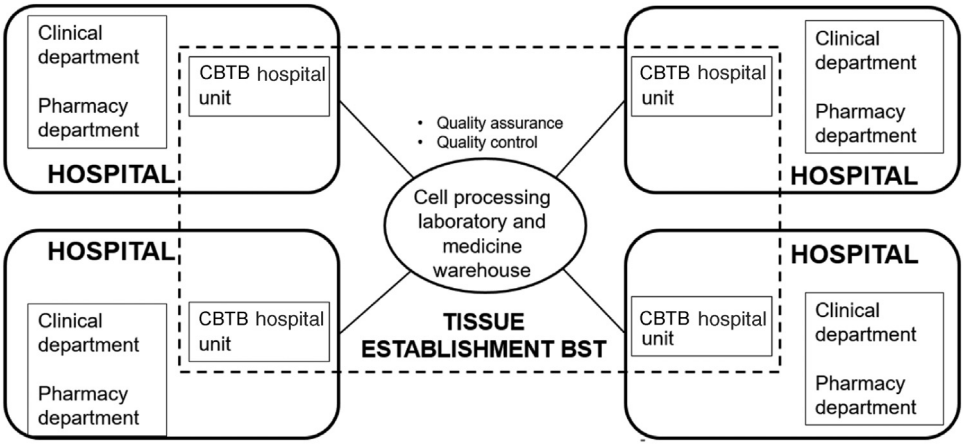

Fig. 2. Relationship between CTPL and cryogenic medicine warehouse (hub) and each hospital (clinical and pharmacy departments and Catalan Blood and Tissue Bank hospital units/spokes). Catalan Blood and Tissue Bank hospital units provide cell collections and CAR T-cell thawing. The hospital is represented by a solid line and the tissue establishment (Catalan Blood and Tissue Bank) is represented by a dashed line. BST, Banc de Sang i Teixits.

plus two backup) and four centers to treat pediatric patients (three nominal plus one backup) with authorized CAR T-cell medicinal products. Owing in part to this model, four of the 10 designated adult and two of the four designated pediatric centers were hospitals affiliated with the Catalan Blood and Tissue Bank CTPL [16]. As CAR T cells are a medicinal product, they fall under the responsibility of clinical pharmacists. In order to guarantee the legal provisions, the Catalan Blood and Tissue Bank hub was authorized as a medicinal product warehouse for cryogenic products by the Catalan Health Authority. Figure 2 describes the specific relationship established between hospitals and the Catalan Blood and Tissue Bank for CAR T-cell activities.

Quality Management System

The hub-and-spoke model allows common standardization of quality management systems, including operating procedures, computer systems, training and quality assurance. Logistics, such as product transportation within the network, is done using dedicated drivers for all hospitals. A single master quality manual defines all workflow for the management of externally manufactured CAR T-cell products and the relationship with stakeholders (clinical team, pharmacy team and manufacturers). The minimum requirements for all manufacturers are described in the master standard operating procedure (SOP). The apheresis and handling manuals for CAR T cells from manufacturers are incorporated as external documentation in the Qualiteasy 7.21 electronic quality management system (Qualiteasy Internet Solutions S.L., Barcelona, Spain). The specific SOPs are also available for hospital counterparts (clinical unit and pharmacy service) on a shared intranet. A technical quality agreement is established between sites (public hospital network), the Catalan Blood and Tissue Bank (authorized tissue establishment) and sponsors (manufacturers) with defined responsibilities. Finally, a document with track changes is opened with each new clinical trial, analyzing the manufacturer's requirements and assessing the risk of each change.

CAR T-Cell Supply Chain and Activity

Cell collection

Leukocytapheresis is performed at Catalan Blood and Tissue Bank units located in each hospital under an authorization provided by the local competent authority for cell collection. This activity is further regulated by an agreement between the Catalan Blood and Tissue Bank and the hospitals, where the roles and responsibilities of each party are defined. All collection centers are JACIE-accredited. The apheresis staff is composed of a medical director, a deputy hematologist, a nursing team and a quality assurance technician.

Clinical trials with CAR T cells started in 2016, and since then they have grown exponentially, from one trial in 2016 to 10 in 2021 (Figure 3A). During this period, a total of 348 autologous cell collections were procured as starting materials for CAR T-cell therapies, 153 (44%) of which were for clinical trials, with an exponential increase over the years (Figure 3B). In April 2019, three of 10 adult and two of four pediatric centers designated by the Spanish management plan and technically qualified by manufacturers were academic hospitals affiliated with the Catalan Blood and Tissue Bank, resulting in an explosion of activity for commercial CAR T-cell products. One year later, and with manufacturers' technical qualifications acquired by most of the designated centers, activity related to commercial CAR T-cell medicinal products reached a plateau.

Processing and shipping of starting materials

All manufacturers but one require fresh starting material. Accordingly, during the study period, 199 (61%) of a total of 348 leukocytapheresis collections were frozen and transported cryopreserved. For cryopreservation, apheresis products were transferred by car (between 15 min and 30 min) to the CTPL located in the Catalan Blood and Tissue Bank hub facility from any of the six hospitals with a CAR T-cell program. A specialized courier service guarantees secure and rapid transport between collection centers and the CTPL.

The CTPL is a JACIE-accredited cell processing laboratory. The staff is composed of a medical director, a deputy hematologist, a technical director, a quality assurance technician, two laboratory supervisors and seven technicians (in two shifts). Processing of starting materials is performed in a class D clean room equipped with two biological safety cabinets, two controlled-rate/programmable freezers and two dedicated vapor phase liquid nitrogen tanks located in a separate cryogenic room.

Receipt, storage and distribution of manufactured CAR T-cell medicinal products

Once manufactured and released, CAR T-cell products are sent back to the Catalan Blood and Tissue Bank cryogenic medicine warehouse (hub). Receipt of the product is recorded (verification of integrity, certificate of conformity by qualified individual, traceability, in-transit temperature), and it is then stored at a cryogenic temperature within the cryogenic medicine warehouse facility on behalf of each hospital pharmacy service according to a specific agreement, with defined roles between each hospital pharmacy and the Catalan Blood and Tissue Bank.

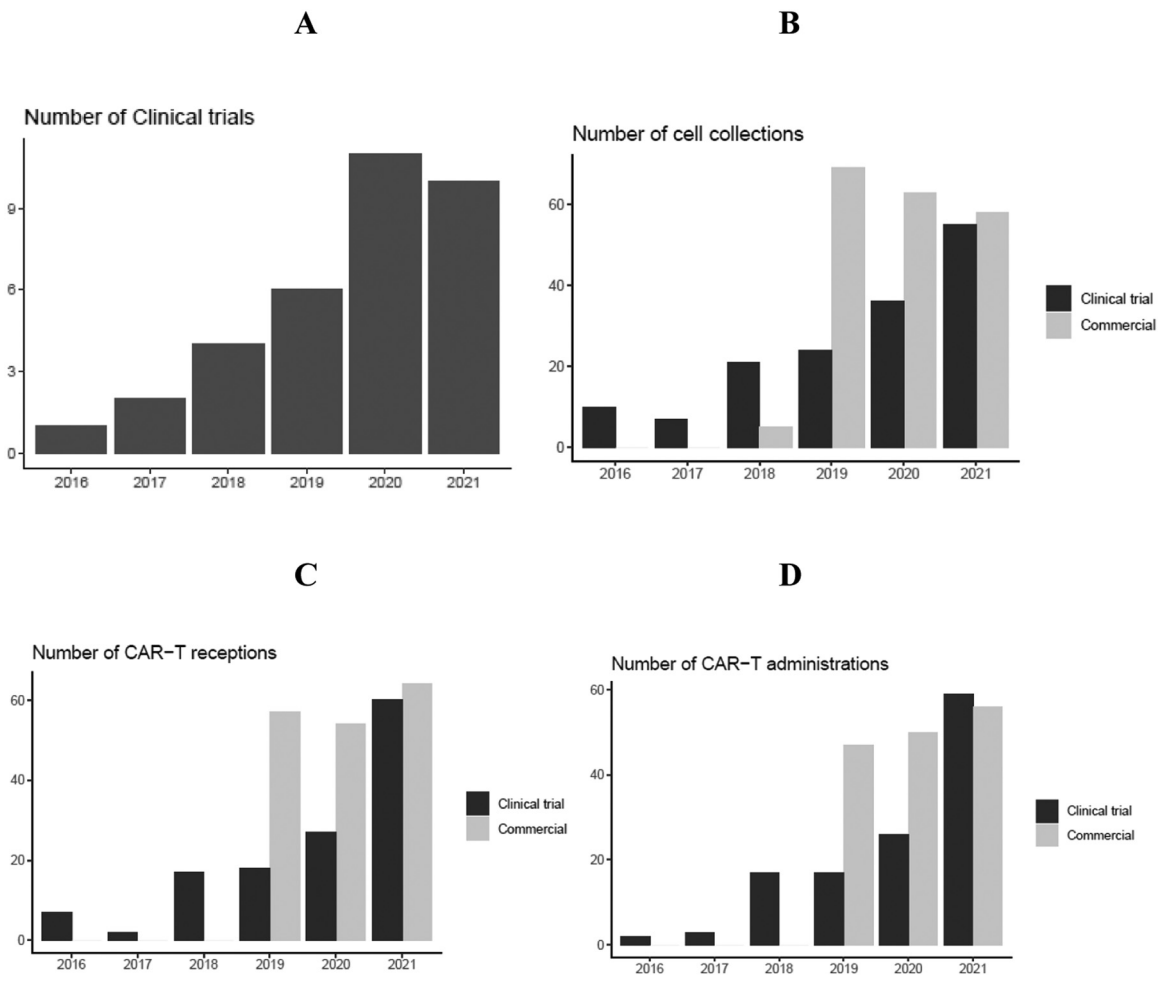

Fig. 3. CAR T-cell activity at the Catalan Blood and Tissue Bank from 2016 to 2021. (A) Number of CAR T-cell clinical trials per year. (B) Number of cell collections procured as starting material for clinical trials and commercial CAR T-cell therapies per year. (C) Number of CAR T-cell collections received at the Catalan Blood and Tissue Bank cryogenic medicine warehouse. (D) Number of clinical trial and commercial CAR T-cell infusions per year.

During the study period, the Catalan Blood and Tissue Bank received 313 CAR T-cell medicinal products from different manufacturers, with a significant increase over the years (Figure 3C). Of these, 180 (58%) were commercial CAR T-cell products. CAR T-cell medicinal products are stored cryopreserved at the Catalan Blood and Tissue Bank cryogenic medicine warehouse until the day of infusion, when they are sent to the hospital upon confirmation of patient suitability for treatment by the clinical team. The product is placed in a dedicated and validated dry shipper with a controlled temperature and transported by trained couriers.

Thawing and administration of CAR T cells

Once the CAR T cells are received at the Catalan Blood and Tissue Bank hospital units, they are jointly verified by Catalan Blood and Tissue Bank staff and the pharmacy team. Thawing is performed by the Catalan Blood and Tissue Bank team under the supervision of the pharmacy team in a water/dry bath device according to the manufacturer's requirements. Once the CAR T cells are thawed, the product is transported in a validated box with a controlled and monitored temperature to the clinical unit and administered by the clinical team within 30 min of thawing. As of 2021, 281 CAR T-cell products had been thawed and infused (Figure 3D), 155 (55%) of which were commercial CAR T-cell products.

Discussion

In order to provide access to CAR T-cell therapy within the public health care system, and using a supply chain similar to that employed for HSCT, the Catalan Blood and Tissue Bank consolidated hub-and-spoke model was proposed to support the CAR T-cell therapy program in six public hospitals in Catalonia, Spain. Because of the Catalan Blood and Tissue Bank's JACIE-accredited collection and cell processing program, collaborative stakeholders with regular JACIE meetings, high activity in apheresis and processing and implementation of CAR T-cell SOPs, this model contributed to the early designation of centers according to criteria established in the Spanish management plan. Consequently, four of the 10 hospitals designated to treat adult patients and two of the four hospitals designated to treat pediatric patients with CAR T cells were affiliated with the Catalan Blood and Tissue Bank. Accordingly, this integrated structure allowed rapid technical qualification, and five of the six designated Catalan Blood and Tissue Bank-affiliated hospitals were already accredited by manufacturers when the Spanish management plan designated the centers in April 2019.

The hub-and-spoke model provides a networking system of care anchored by an established full-service care center (hub) complemented by secondary establishments (spokes) that offer more limited services but alleviate acute shortages in care. Some examples of hub-and-spoke models are traditional single regional blood centers that receive all blood donations in one region, which is fractionated into blood components and then provided to the hospitals for transfusion,

or centralized treating hospitals for specific diseases such as sickle cell [18]. This model emerged as the most cost-effective method with the highest quality and safety with regard to health care services. Following this model, peripheral blood mononuclear cell collection, cell processing and distribution are often implemented in blood bank working units. In a survey of how ATMPs were accommodated in academic hospitals, 78% of respondents answered that their CTPL supported externally manufactured investigational products as per this model [15].

The workflow of the CAR T-cell process requires complex procedures, and logistics for the successful delivery of safe products to patients is challenging. A well-experienced, qualified CTPL plays a critical role in ensuring the proper handling and safety of products, taking care of all required steps, from the academic center to the manufacturer to, finally, the patient for infusion. Moreover, the rapid expansion of industry-sponsored clinical trials using investigational products has had a significant impact on ensuring the success of each clinical trial. For example, diverse requirements from manufacturers, such as repeat technical qualification and different procedures for procurement and handling, require investment in new equipment and specific training of personnel. As a response to these challenges, a centralized hub-and-spoke model may facilitate efficient access to new CAR T-cell products in a model closely integrated with all stakeholders (clinical and hospital pharmacy units and different ATMP manufacturers).

CAR T-cell medicinal products are shipped frozen and require specialized cryogenic technologies for proper storage and handling. Therefore, an important addition was the creation of a centralized medicinal product warehouse associated with the CTPL for the receipt of final products and their handling, storage and distribution on behalf of the academic pharmacy team [19]. Other hospitals, such as the Mayo Clinic, have also set up administrative units to provide specialized services for industry sponsors manufacturing outside their institution [20]. Therefore, the absence of inter-hospital variability in SOPs is guaranteed and leads to better workflow efficiency, as reported by Joules et al. [21]. Furthermore, resources for bringing new cell therapy products to patients are centralized in a single facility, thereby reducing the financial burden on the public health system.

Conclusions

In the authors' experience, the hub-and-spoke model efficiently supported externally manufactured CAR T-cell products to be introduced in academic public hospitals. This facilitated hospital selection within the CAR T-cell Spanish management plan and permitted early technical qualification by industry of five of six Catalan Blood and Tissue Bank-affiliated centers. Defined role responsibility between key stakeholders is necessary to manage the complexity of the entire process. This model allows patients rapid and easy access to existing and new CAR T-cell therapies, avoids inter-hospital variability, facilitates site technical qualification and provides highly skilled and experienced staff, thereby reducing the work and resources required for ready access to innovative therapies and improving the efficiency of the overall supply chain.

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Author Contributions

Conception and design of the study: JF, JD, JV, LR, AM, CA and SQ. Acquisition of data: JF and AG. Analysis and interpretation of data: JF, JD, JV, LR, AM, CA and SQ. Drafting or revising the manuscript: JF, JD, JV, LR, AM, CA, EV, LM, NR, ML, SA, NG, EG, AA, LM and SQ. All authors have approved the final article.

Declaration of Competing Interest

JF and SQ have served on an advisory board for Novartis.

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