Literature review

Apheresis collection for chimeric antigen receptor T Cell manufacturing: current practices and future directions

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Introduction

Chimeric antigen receptor (CAR) T cell therapy represents a paradigm shift in cancer immunotherapy, offering durable remissions for patients with relapsed or refractory hematologic malignancies[1]. This personalized therapeutic approach involves genetic modification of a patient's own T cells to express CARs, artificial receptors that enable specific recognition and elimination of cancer cells expressing target antigens[2]. Since the approval of the first CAR T cell products in 2017, several therapies have become available for the treatment of B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, and multiple myeloma[3,4]. The successful implementation of CAR T cell therapy depends on a complex manufacturing process that begins with the collection of autologous T cells through leukapheresis[5]. This critical first step provides the cellular starting material for all subsequent manufacturing procedures, including T cell activation, genetic modification, expansion, and formulation. The quality and composition of the leukapheresis product directly influence the characteristics of the final CAR T cell product and, consequently, its clinical efficacy and safety profile[6].

Despite its fundamental importance, standardization of apheresis procedures across institutions remains challenging, with variations in collection protocols, equipment, and quality control measures[7]. Factors such as patient characteristics, disease status, prior treatments, and technical considerations all contribute to variability in the apheresis product, potentially impacting downstream manufacturing success[8]. This review aims to provide healthcare practitioners with a comprehensive understanding of apheresis collection for CAR T cell manufacturing. We examine current practices, technical considerations, quality control parameters, challenges encountered in different patient populations, and emerging strategies to optimize this crucial process. As CAR T cell therapy continues to expand into new indications and treatment settings, a thorough understanding of apheresis collection becomes increasingly relevant for hematologists, oncologists, apheresis specialists, and other healthcare providers involved in the care of patients undergoing this transformative therapy.

Current practices in apheresis collection

Principle of leukapheresis

Leukapheresis involves the selective removal of leukocytes from peripheral blood while returning other blood components to the patient[9]. This process utilizes continuous-flow centrifugation to separate blood components based on their density, allowing for the collection of mononuclear cells (lymphocytes and monocytes) that contain the T cells required for CAR T cell manufacturing[10]. The separation of blood components depends on their specific gravity: red blood cells (1.08-1.10 g/mL) are the heaviest, followed by granulocytes (1.075-1.085 g/mL), mononuclear cells (1.065-1.075 g/mL), platelets (1.040-1.060 g/mL), and plasma (1.025-1.029 g/mL), respectively[11]. During leukapheresis, careful adjustment

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of the collection interface allows for selective harvesting of the mononuclear cell layer while minimizing contamination with other cellular components. Modern apheresis devices employ automated interfaces that optimize cell separation and collection efficiency. The two predominant platforms used for CAR T cell collection are the Spectra Optia (Terumo BCT) and the COBE Spectra (Terumo BCT) systems[12]. These platforms differ in their collection mechanisms, with the Spectra Optia utilizing an automated interface management system that potentially offers improved consistency and reduced operator dependency compared to the semi-automated COBE Spectra[13].

Pre-apheresis considerations

Patient evaluation prior to apheresis collection is crucial for optimizing outcomes. Timing of collection is an important factor, as scheduling apheresis during periods of disease stability is preferred. High disease burden may contaminate the product with malignant cells[14]. In B-cell malignancies, the presence of circulating malignant B cells can introduce CD19+ tumor cells into the product, potentially leading to manufacturing contamination or contributing to antigen escape mechanisms. Recent therapies can substantially impact collection outcomes. Certain chemotherapeutic agents and immunosuppressive medications can affect T cell quantity and quality. Alkylating agents such as cyclophosphamide and bendamustine cause prolonged lymphodepletion, while purine analogs including fludarabine and cladribine induce selective T-cell depletion with potentially long-lasting effects[15]. A washout period of 2-4 weeks following lymphotoxic therapies is generally recommended, though the optimal interval depends on the specific agent and its pharmacokinetic properties.

Adequate vascular access is essential for successful apheresis. Peripheral venous access with 16-gauge or larger needles is preferred for adult patients, allowing flow rates of 50-100 mL/min[16]. Central venous catheters are often required for pediatric patients or adults with poor peripheral venous access, with catheter size selected to accommodate the required flow rates while minimizing recirculation. Baseline hematologic parameters also guide collection strategies. Complete blood count assessment is particularly important, as baseline lymphocyte counts should ideally exceed 0.5 $\times 10^9$/L to ensure sufficient T cell collection, although successful manufacturing has been reported with lower counts[17]. A retrospective analysis by Tuazon, et al. found that pre-apheresis absolute lymphocyte counts strongly correlated with CD3+ T cell yield and was the strongest predictor of meeting target cell doses in a single collection[18].

Standard collection parameters

While collection protocols vary across institutions and CAR T cell products, several parameters have emerged as standard practice. Blood volume processed typically ranges from 2-3 total blood volumes (approximately 8-12 liters for adults) to achieve target cell yields[19]. The relationship between blood volume processed and cell yield follows a logarithmic curve, with diminishing returns after processing approximately 2.5 blood volumes. Collection flow rates typically range from 0.8-1.2 mL/kg/min, with adjustments based on patient tolerance and venous access[20]. Higher flow rates may increase collection efficiency but can exacerbate citrate-related symptoms and mechanical hemolysis. Anticoagulation management is critical during apheresis. Acid citrate dextrose solution A (ACD-A) is the standard anticoagulant, with a typical whole blood to ACD-A ratio of 12:1 to 15:1[21]. Citrate binds calcium ions, preventing coagulation but potentially causing symptoms of hypocalcemia, including perioral paresthesia, nausea, and, rarely, tetany or arrhythmias. Prophylactic calcium supplementation may be administered orally or intravenously, particularly for patients at higher risk of citrate toxicity. Target cell yields vary by product but generally aim for 5-10 $\times 10^9$ total nucleated cells or 1-3 $\times 10^9$ CD3+ T cells[22]. Commercial CAR T cell manufacturing protocols have established minimum cell dose requirements, which incorporate manufacturing losses and establish safety margins to ensure adequate final product doses.

Technical considerations and quality control

Optimizing mononuclear cell collection

Several technical factors influence the efficiency and composition of the apheresis product. Collection interface settings require precise adjustment to optimize mononuclear cell collection while minimizing platelet and granulocyte contamination[23]. The interface position can be visualized directly (COBE Spectra) or monitored via automated optical sensors (Spectra Optia). Even small deviations from optimal settings can significantly alter product composition, with more conservative (lower) offsets increasing red blood cell contamination and more aggressive (higher) offsets increasing platelet and granulocyte contamination. On the COBE Spectra, collection preference settings range from 1-11, with CAR T collections typically utilizing intermediate settings to balance yield and purity. The Spectra Optia employs Collection Preference parameters between 0-40, with most CAR T protocols using midrange settings and leveraging the Auto-Adjust feature that optimizes parameters based on real-time interface conditions. Patient factors, particularly hematocrit levels, further influence these settings, requiring ongoing monitoring and adjustment during collection. Inlet flow rate adjustments can alter the separation dynamics within the centrifuge bowl, affecting the precision of interface positioning[24]. Flow rate adjustments can alter the separation dynamics within the centrifuge bowl, affecting the precision of interface positioning. A balance must be achieved between procedural efficiency and product quality, with typical flow rates of 50-80 mL/min for adults and weight based calculations for pediatric patients.

The patient's hematocrit influences separation dynamics, with higher hematocrits increasing the density differential between cellular components[25]. Procedures may require adjustment for patients with extreme hematocrit values, as these affect the position and thickness of the buffy coat layer. During apheresis, blood components separate based on density differences, with the hematocrit (proportion of red blood cells) directly impacting this separation. In patients with high hematocrit, the dense red cell layer creates a more distinct boundary with the buffy coat (containing target mononuclear cells), potentially improving separation clarity but requiring adjustment of the collection interface position. Conversely, in low hematocrit states, the red cell/buffy coat boundary becomes less distinct, making selective collection more challenging and necessitating modified centrifuge speed or interface offset settings to maintain optimal separation of the target cell population.

Product characterization and quality control

Rigorous assessment of the apheresis product is essential for ensuring suitability for manufacturing. Cell enumeration through complete blood counts with differential and flow cytometric analysis of CD3+, CD4+, and CD8+ T cell subsets provide critical information about product composition[26]. Advanced immunophenotyping may further characterize T cell differentiation states (naïve, central memory, effector memory, terminal effector) and activation status through expression of markers such as CD45RA, CCR7, CD62L, CD27, and CD28.

Viability assessment using trypan blue exclusion or flow cytometry-based viability dyes evaluates cellular health, with targets typically exceeding 85% viable cells[27]. The importance of viability extends beyond simple live/dead quantification, as sublethal cellular damage can impair subsequent manufacturing steps. Product volume and hematocrit affect cell concentration and cryopreservation efficiency, with optimal hematocrit values below 4%[28]. Excessive residual red blood cells can interfere with genetic modification procedures and compromise cryopreservation through hemolysis-induced toxicity. Sterility testing through microbiological evaluation ensures product safety, though results may not be available before initiating manufacturing[29]. Rapid microbial detection methods, including polymerase chain reaction-based approaches and automated culture systems, have been implemented to provide earlier contamination alerts.

Cryopreservation and transportation

Following collection, apheresis products must be properly processed for transport to manufacturing facilities. Initial processing typically involves volume reduction, washing, and concentration to prepare for Cryopreservation[30]. These procedures remove anticoagulants, platelets, and plasma proteins that could interfere with subsequent manufacturing steps. Cryopreservation media containing dimethyl sulfoxide (DMSO) with human serum albumin or other protein supplements protect cells during freezing[31]. Standard formulations include 10% DMSO with 5-6% hydroxyethyl starch and 2-4% human serum albumin, though DMSO concentrations as low as 5% have been successfully employed, reducing toxicity concerns. Controlled rate freezing using standardized protocols minimizes cellular damage from ice crystal formation[32]. Optimal cooling rates typically range from -1°C to -3°C per minute until reaching approximately -40°C, followed by more rapid cooling to storage temperature. Cold chain management with strict temperature monitoring during transport is essential to maintain product integrity[33]. Validated shipping containers maintain temperatures below -150°C using liquid nitrogen vapor, with continuous temperature logging and redundant systems to prevent warming events.

Challenges in special patient populations

Pediatric patients

Apheresis collection in pediatric patients presents unique challenges. Weight-based considerations necessitate careful adjustment of processing parameters and may require priming of the apheresis circuit with irradiated, leukoreduced blood products for very small children. For patients weighing less than 20 kg, circuit priming with compatible blood products prevents excessive extracorporeal volume and reduces the risk of hemodynamic instability[34,35]. Extracorporeal volume limitations typically restrict the maximum allowable extracorporeal volume to 10-15% of the patient's total blood volume, limiting the equipment and protocols that can be safely utilized[35]. This limitation affects the selection of apheresis platforms, with devices offering reduced extracorporeal volumes preferred for smaller patients. Priming blood for pediatric patients generally requires warming to body temperature (37°C) to prevent hypothermia, which is particularly important in small children whose limited blood volume and immature thermoregulatory mechanisms make them susceptible to temperature-related complications. This warming process is typically accomplished using blood warmers integrated into the return line of the apheresis circuit, ensuring that blood components maintain appropriate temperature as they re-enter the patient's circulation, thereby reducing the risk of hypothermia-related complications such as cardiac arrhythmias, metabolic acidosis, and coagulation abnormalities.

Vascular access limitations due to smaller vessel diameter often necessitate central venous access, increasing procedural complexity[35]. The placement and management of central venous catheters in pediatric patients require specialized expertise, with potential complications including infection, thrombosis, and mechanical dysfunction. Psychological support through age-appropriate preparation and distraction techniques are important components of the pediatric apheresis experience. Specialized approaches include medical play therapy, virtual reality distraction, and dedicated child life specialist involvement[36].

Heavily pre-treated patients

Patients with relapsed/refractory disease often have compromised hematopoietic function. Lymphopenia can necessitate prolonged or repeated collections[37]. Absolute lymphocyte counts below 0.3 $\times 10^9$/L are associated with significantly reduced collection yields, with each 0.1 $\times 10^9$/L increase in pre-apheresis count corresponding to approximately 0.5 $\times 10^9$ additional CD3+ cells collected. T cell dysfunction from prior therapies can induce phenotypic and functional alterations in T cells, including increased expression of exhaustion markers (PD-1, TIM-3, LAG-3) and reduced proliferative capacity[38]. These changes may

persist despite adequate numerical recovery, affecting downstream manufacturing outcomes. Alternative collection strategies may be necessary in challenging cases. Bone marrow harvesting has been explored as an alternative source of T cells when peripheral blood collection is suboptimal[39]. While technically feasible, bone marrow-derived T cells exhibit different phenotypic characteristics compared to peripheral blood T cells, including lower proportions of effector memory cells and different cytokine production profiles.

Patients with comorbidities

Certain medical conditions complicate the apheresis process. Cardiovascular disease, particularly significant cardiac dysfunction, may limit tolerance to rapid fluid shifts, requiring modified collection parameters[40]. Reduced inlet flow rates, careful management of fluid balance, and continuous cardiac monitoring help mitigate risks in this population. Renal impairment affects citrate metabolism, increasing the risk of citrate toxicity during apheresis[41]. Patients with estimated glomerular filtration rates below 30 mL/min/1.73m^2 typically require reduced citrate infusion rates and more frequent ionized calcium monitoring. Hepatic impairment also significantly impacts this process, as the liver is the primary site of citrate metabolism. In patients with compromised liver function, reduced citrate clearance leads to increased accumulation and prolonged hypocalcemia effects, requiring modified anticoagulation strategies and more stringent calcium monitoring. Hyperleukocytosis in patients with very high white blood cell counts may require leukoreduction prior to CAR T cell manufacturing to prevent overwhelming downstream processes[42]. White blood cell counts exceeding 50 $\times 10^9$/L can interfere with mononuclear cell separation during apheresis, resulting in suboptimal product composition.

Emerging strategies and future directions

Novel collection technologies

Technological innovations are enhancing apheresis efficiency and product quality. Microfluidic separation through lab-on-chip technologies offers precise control over cell separation with reduced sample volumes[43]. These approaches may enable more selective T cell subset isolation while minimizing contamination with non-target cells. Immunomagnetic selection for direct isolation of T cell subsets during apheresis may streamline manufacturing and enhance product consistency[44]. Integrating immunomagnetic selection into the apheresis procedure could reduce manufacturing time and improve final product characteristics. Enhanced interface control through advanced optical sensors and machine learning algorithms is improving the precision of interface management[45]. These technologies adapt to individual patient characteristics, optimizing separation parameters in real-time to maximize target cell collection.

Pre-apheresis optimization strategies

Several approaches aim to improve starting material quality. Timed collections coordinated with circadian variations in lymphocyte trafficking may optimize yields[46]. Emerging evidence suggests that lymphocyte counts and subset distributions exhibit diurnal variations, potentially affecting collection efficiency. Selective lymphocyte mobilization through novel agents that preferentially mobilize specific T cell subsets into peripheral circulation could enhance starting material composition[47]. Preclinical studies are exploring compounds that target lymphocyte trafficking pathways to enrich for desirable T cell phenotypes.

Standardization efforts

Initiatives to harmonize apheresis practices are gaining momentum. International consensus guidelines developed by professional societies are establishing standardized recommendations for CAR T cell collection[48]. These efforts aim to establish minimum standards for equipment, procedures, and quality control measures across institutions. Quality metrics establishing universal quality parameters facilitate cross-institutional comparison and process improvement[49]. Standardized reporting of collection efficiency, product composition, and manufacturing outcomes enable identification of best practices.

Conclusion

Apheresis collection represents a critical determinant of CAR T cell therapy success. The process demands careful consideration of patient factors, technical parameters, and quality control measures to ensure optimal starting material for manufacturing. As CAR T cell therapies expand into new indications and treatment settings, standardization and optimization of apheresis practices become increasingly important. Future advances in collection technology, pre-apheresis optimization strategies, and quality control methods promise to enhance the consistency and efficacy of the apheresis product. Healthcare practitioners involved in CAR T cell therapy should maintain awareness of evolving best practices in apheresis collection to ensure optimal outcomes for their patients.

The successful implementation of CAR T cell therapy within clinical practice requires interdisciplinary collaboration among hematologists, oncologists, apheresis specialists, cell processing technologists, and nursing staff. With continued refinement of apheresis collection practices and emerging innovations, the foundation of CAR T cell manufacturing will strengthen, ultimately improving outcomes for patients undergoing this transformative therapeutic approach.

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