Collection of Mononuclear Cells for Immune Effector Cell Therapies

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MARCH 5, 2019
REPRESENTING THE AMERICAN SOCIETY FOR APhERESIS
Recently, the FDA approved two CAR T-cell products

- **Yescarta** *(axicabtagene ciloleucel)*
  - Treatment of diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBC)

- **Kymriah** *(tisagenlecleucel)*
  - Treatment of acute lymphoblastic leukaemia (ALL) and DLBCL

Furthermore, there are many recent clinical trials with Immune Effector Cells (IECs)
Collection facilities are required to collect mononuclear cells (MNCs) as the first step in obtaining the raw materials to produce licensed products or IEC trials.

Apheresis sites are noticing the inconsistencies in procedures for the apheresis collection of MNCs.

Goal of apheresis in clinical manufacturing context:
- Have a consistent, robust process optimal for the therapeutic product
- Ensure safety and comfort of the donor
Goals of Apheresis Collection

- For hematopoietic progenitor cell collections or donor lymphocyte infusions, most accreditation agencies (i.e., AABB, FACT) have standards requiring a written order to include goals of collections
  - # CD34 cells/kg of recipient
  - # CD3 cells/kg of recipient
- Not the case with many sponsors for collection of MNCs for production of CAR T-cells and other IEC products
- In fact, some of the manufacturers simply ‘recommend’ a wide range of total blood volume (TBV) to be processed at the time of collection
  - 12-15 L
  - 2-4 x TBV
Pre-Apheresis Collection Assessments for IECs

- No assessment of donor suitability based on total nucleated cell (TNC) and/or CD3 pre-apheresis collection counts
- Leaves room for interpretation for collection staff
- No clear guidance of what will be the implication of choosing one or the other will be for the final product
- This is problematic
  - No certainty of obtaining appropriate numbers of target cells via apheresis
  - These cells critical to manufacturing process and therapeutic outcome
Examples of Guidance from Product Manuals

- **Yescarta**
  - Apheresis cell collection target goal of approximately $5-10 \times 10^9$ MNCs
  - Which is approximately 12-15 L (TBV processed), but can be more or less based on the patient's weight
Examples of Guidance from Product Manuals

- **Kymriah**
  - Minimum goals of TNC $\geq 2.0 \times 10^9$ or CD3 cells $\geq 1.0 \times 10^9$
  - To ensure cell count minimums are met, an adequate volume of blood needs to be processed during leukapheresis collection
    - Generally 2-4 $\times$ patient TBV
  - If collection efficiency and peripheral CD3 lymphocyte count is known, the estimated minimum blood volume to be processed can be calculated

- With the collection of this product, you can try to predict the number of TBVs based on peripheral TNC or CD3 count and the collection efficiency of your apheresis device
Different Rules Applied at Different Centers

- All too often the targeted cell dose is not given → Inconsistencies
- # TBVs is typically used
  - Creates its own inefficiencies as patients kept on apheresis devices longer than needed just to ensure that “adequate product cellularity” is obtained in fewest collections possible
- We would like to see that peripheral count assessments specific to the product be mandatory prior to apheresis collection
  - This is to ensure ample starting materials for IEC production
  - To protect donors from unnecessary and/or prolonged collections
    - Attendant risks of apheresis collection procedures
  - To prevent collection failures
Future Products

- We are certain that these two FDA-licensed CAR T-cell products are just the start.
- Many other IEC products are anticipated to seek FDA-approval over the next few years.
- We want to make this as safe and efficient a process as possible for all.
Desired Outcome

- **Require specific goals** for collection of cells for production of CAR T-cells and other IEC products, e.g., number of cells needed to start a successful manufacturing process

- Doing so will
  - **Reduce variability** in starting materials for IEC products
  - **Optimize quality** of collections
  - **Enhance safety** of our donors by eliminating unproductive collections, longer collections than necessary, and collection failures
  - **Allow collection of products** with optimal target cell counts and low presence of contaminating cells in a minimal volume