Collection of Mononuclear Cells for Immune Effector Cell Therapies

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REPRESENTING THE AMERICAN SOCIETY FOR APHERESIS

New Products

- 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 (PMBCL)
  - **Kymriah** (tisagenlecleucel)
    - Treatment of acute lymphoblastic leukaemia (ALL) and DLBCL
- Furthermore, there are many recent clinical trials with Immune Effector Cells (IECs)

Apheresis Collection Facilities

- 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 x 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 ≥ 2.0 x 10^9 or CD3 cells ≥ 1.0 x 10^9*
  - *To ensure cell count minimums are met, an adequate volume of blood needs to be processed during leukapheresis collection*
    - *Generally 2-4 X 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