Development of Stability Program at a Cord Blood Bank

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Current practice does not require assigning expiration date to cord blood units

Limited published data:
Background

- **New York Blood Center Data** (being presented at ASH meeting) -
  *Personal communication: Dr. Machi Scardavou*

**Outcome data for patients receiving NYBC units:**

*Units stored for ≥8 years (N=43, median storage time: 9.2 years) compared to units stored <2 years (N=300, median storage time: 1.1 years)*

- Time to ANC recovery, graft failure rate and overall survival were no different between the two groups
Why the Recent Interest in CB Stability?

Draft FDA Guidance- December 2006:

- Applicable to Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies

- Recommendations for manufacturers for submission of a biological license application (BLA)
Draft FDA Guidance- December 2006:

**Stability Testing (21 CFR 211.116)**

“There must be a written testing program designed to assess the stability characteristics of HPC-C. Stability program should include……analyses of product potency, integrity and sterility…..Results of such testing must be used in determining appropriate storage conditions and expiration dates”

Program must include:

- Sample size and test interval
- Storage condition
- Reliable, meaningful and specific test methods
- Testing of the HPC-C in the same container-closure system as that in which the HPC-C is marketed
- Adequate number of HPC-C must be tested to determine an appropriate expiration date
WHAT SHOULD WE DO NOW?

- Send your comments to FDA on the draft guidance and hope for the best
- Start developing a plan
Product Information

- Cord blood collected from volunteer donors
- Processed and stored within 48 hours of collection
- Buffy coat separation performed using hydroxyethyl starch
- Cryopreservation in Pall bags with final DMSO concentration 10%

Segments (~ 0.1mL each)

20mL fraction

5mL fraction
Product Information

- Final volume in bag: 25 mL
- Over-wrapped
- Control-rate freezing using Bioarchive system (Thermogenesis)
- Stored in liquid phase of Liquid Nitrogen
Challenges

- Two buffy coat processing methods
  - Manual centrifugation
  - Automated Sepax (Biosafe SA)
- Cell concentration (wide range)
- Oldest unit in bank is 28 months old (Bank established April 2005, >2900 units banked)
- Limited # of units available that are >2 years old
- Plan will result in sacrificing units from minority donors
Testing & Analysis

Pre-cryopreservation and Post-thaw

- Sterility (Bactec)
- Nucleated cell count (automated cell counter)
- CD34 analysis
- Viability (flow cytometry, 7AAD)
- Colony forming unit assay
- Visual inspection
3-Part Proposed Plan

Part I: Retrospective testing
   Evaluating units already stored

Part II: Prospective testing
   Storing units for purpose of stability evaluation

Part III: Clinical Outcome Analysis
   As data becomes available on transplanted units
Variables

- Automated versus Manual Processing Method
  *Not included in plan- data from both methods has shown equivalent products*

- Cell Concentration
  *To avoid loss of units with high nucleated cell count, majority of units selected for testing may have lower cell concentration*
Part 1: Retrospective Testing

- # of units to be tested for each year: 10 (oldest unit: 2 years)
  - Use either the 20% or 80% fraction
  - Some later time, will use the other fraction
- Quality control parameters evaluated over time, up to 10 years:
  - Total of 100 units needed
  - Using the two fractions for evaluation, reduces the # to 50
  - May be used to compare results from two fractions
- If 10 year data acceptable, continue for additional years
- Additional units tested yearly
Part 2: Prospective Testing

- Projected # of units to be collected annually: 2500

- # of units to be stored for testing: 25 (1% of total)

  - Within 30 days from storing:
    - Segment thaw for viability and CFU testing - Baseline
  
  - Year 5: 5mL fraction thaw (5-year stability)
  
  - Year 10: 20mL fraction from same unit tested (10-year stability)
Part 3: Clinical Outcome Data

- Evaluation of engraftment data
- Analysis based on unit age
- Extended over several years to obtain sufficient number of data
Unit Selection Concerns

- Loss of units from minority donors

Goal is to store as many as possible….

- Should random selection of units be avoided?
- If excluded, can stability data apply to these units as well?

MD Anderson Minority Allo Transplant

- BM and PBPC Transplants (n=3038) 1980-2003
- CB Transplants (N=105) 1996-2004

- Caucasian
- Non-caucasian
Unit Selection Concerns

- Loss of units with high TNC
  Acceptable units for HRSA must have \( \geq 0.9 \times 10^9 \)
  Total Nucleated Cells….

  - Should random selection of units be avoided?
  - If excluded, can stability data apply to these units as well?
Plan Implementation

- Ensure plan meets the requirement for BLA submission
- Advance review and acceptance of plan by FDA
Summary

- Stability testing program at each Cord Blood Bank may be different.
- Number of units available, age and type of units should be considered in program development.
- Since each unit is truly a single batch, banks face unique challenges when developing a stability program.
- Early discussion with FDA is extremely important.
- Minimizing loss of very valuable units for clinical transplantation should be considered.
- Can published clinical outcome data be used in support of stability testing?