The Increasing Role of Leukapheresis Collections

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Objectives

• Review types of leukapheresis procedures
• Highlight specific characteristics of leukocyte collections in apheresis programs
• Review challenges of leukocyte collections
The Leukocyte
History of Leukapheresis

• Dr Carl De Laval invents hand-cranked cream separator in 1877
• Edwin J. Cohn develops centrifugal blood separator in 1951
• Emil Freireich develops NCI-IBM 2990 & IBM 2997 blood separator for use in leukemic patients in 1963 & 1973
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Collections

- Stem Cell collections (HPC)
- Lymphocyte collections (DLI’s)
- Granulocyte collections
- Bone Marrow Processing
- MNC collections
- Research leukocyte collections

Therapeutic Procedures

- TPE / Plasma Exchange
- Photopheresis
- Red Blood Cell exchange
- Leukocyte depletions
- Thrombocyte depletions
- Plasma adsorption
Carter BloodCare
Clinical Apheresis
Procedures FY 2010

Total Procedures: 1720

WBC Collect 307 (18%)

TPE 1226 (71%)

Other 294 (11%)
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Clinical Apheresis
Procedures FY 2011

Total Procedures: 2002

WBC Collect
475 (24%)

TPE
1427 (71%)

Other
101 (5%)
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Clinical Apheresis
Procedures FY 2012

Total Procedures: 1975

WBC Collect 654 (33%)

TPE 1228 (62%)

Other 93 (5%)
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Clinical Apheresis
Procedures FY 2013

Total Procedures: 2104

WBC Collect 702 (33%)

TPE 1289 (61%)

Other 113 (5%)
Donor vs. Patient

- Is it really a donor or a patient?
- Does it fall under donor procedures/collections or therapeutic apheresis?
- Tradition line between donor apheresis and therapeutic apheresis still exist?
- New CT products, remove cells that turn it into a therapeutic vaccine
Questions to “ponder”?

• What’s the difference between therapeutic and donor apheresis?
• Where do HPC’s fit in?
• Are HPC’ donors really donors or patients?
• What about dendritic cell collections, donors or patients?
• Is photopheresis a type of therapeutic apheresis or not?
• Some donors are stimulated, does this change how we regard them as donors or patients?
• Why is there so much more paperwork necessary for stem cell collections compared to TA procedures?
Hematopoiesis: maturation process for Leukocytes
Granulocyte Collections

- **Hx:** CML patients collected; cells used for transfusion
- **Target cell =** mature granulocytes
- **Sedimenting agent –** hetastarch added to apheresis circuit
- **Need to stimulate donors:**
  - with corticosteroids or Neupogen
- **24 hour expiration**
- **Yield –** $1 \times 10^{10}$
Stem Cell Collection “HPC”

- Leukapheresis collections to “harvest” the immature cells used for BMT
- Target Cell = Pluripotent Stem Cell
- Autologous and Allogeneic
- Unrelated: National Marrow Donor Registries
- Allos – Cytokine stimulation
- Autos: Chemotherapy &/or mobilization agents
- Dose: 5 x 10E6 CD34 per kg
Lymphocyte Collections

- Donor Lymphocyte Infusions – usually from bone marrow donor
- Target cell: mature lymphocytes
- Goal: induce graft-versus-tumor effect (GVT) for remission of cancer
- Donors = Unstimulated
- Dose: $1 \times 10^7$ – $1 \times 10^8$ CD3 per kg
Dendritic Cells (Monocyte collections)

- Target cell: Monocytes
- “raw product” used to manufacture autologous anti-cancer vaccine
- Donors/patients are unstimulated
- MNC collection is performed on blood cell separator
- Target dose: ?
- FDA registration: Somatic Cell Collections
Mechanism of Action

THE PROVENGE PROCESS

DAY 1
LEUKAPHERESIS PROCEDURE
- Resting APC

DAY 2–3
PROVENGE IS MANUFACTURED
- PAP-GM-CSF antigen combines with resting APC
- APC takes up the PAP-GM-CSF
- PAP-GM-CSF is processed and presented on the surface of the APC
- PAP-GM-CSF–loaded APCs are now the active component of PROVENGE

DAY 3 OR 4
PATIENT INFUSION WINDOW
- Inactive T cell
- PROVENGE activates T cells in the body
- Active T cell

The precise mechanism of action of PROVENGE is not known.
Bone Marrow Processing

• “Buffy Coat collection of marrow
• Source: Bone Marrow
• Concentration of cells/volume reduction
• ABO Incompatibility/red cell reduction
• Average 10 per year
  – Easy procedure, but differences marrow and peripheral blood
  – Competency is an issue
Photopheresis

• Combination of leukapheresis with photo-chemotherapy to promote immune balance/tolerance
• Easy procedure to perform
• Unique aspects: uses Heparin for anticoagulant
• No cells are removed: given back to patient at end of procedure
• Therakos only provider in US
  – 2 Machines: XTS & Cellex
• Diseases:
  - CTCL
  - BMT related GVHD
  - Solid Organ rejection
The THERAKOS Photopheresis Procedure

The photoactivated white blood cells are returned to the patient

Photoactivation with UVA light

Methoxsalen

White blood cells are treated with methoxsalen and exposed to UVA light

Blood is separated by centrifugation and red blood cells are returned

The UVAR® XTS™ Instrument draws blood from the patient

UVA = ultraviolet A radiation
THERAKOS Photopheresis: Meaningful Results for CTCL Patients

Before ECP

After ECP
Leukapheresis (AKA WBC Depletion)

• Acute vs Chronic Leukemia
  – Granulocyte, Lymphocytes, or other cells (blasts)

• Purpose: Decrease risks of vascular occlusion (CNS, respiratory, or renal)
  – Tumor Lysis syndrome

• Urgency: Level of symptomatology
  – Presence of Leukostasis
  – Number of Procedures performed:
    • Mobilization, production rate of bone marrow, & chemotherapy initiation
Who are our donors / patients?

- Setting: varies from outpatient clinic or donor center to critical care unit
- In patients – outpatients
- Scheduled procedures vs. last minute “necessary”
- Pediatrics – Geriatrics
What machines do we use?

- Cobe Spectra (15)
- Caridian Optia (7)
- Therakos XTS – UVAR (2)
- Fenwal Amicus (8)

• Ancillary equipment: blood warmers (12)
Technical Aspects of Leukapheresis

PATIENT + anticoagulant

MACHINE + blood

- Desired component removed

+ Replacement Fluid

= Procedure Completed
Centrifugal Apheresis

Plasma
(1.025-1.029)

Platelets
(1.040)

Lymphocytes
(1.050-1.061)

Monocytes
(1.065-1.069)

Granulocyte
(1.087-1.092)

RBC
(1.078-1.114)
Separation: Specific

- Plasma (1.025 - 1.029)
- Platelets (1.040 - ?)
- T-Lymphocytes (1.050 - 1.061)
- B-Lymphocytes
- Blasts: Promyelocytes (1.058 - 1.06)
- Monocytes: Basophils
- Myelocytes: Basophils
- Reticulocytes (1.078)
- Metamyelocytes (1.080)
- Band and Segmented Neutrophils (1.087 - 1.092)
- Erythrocytes (1.078 - 1.114)
- Aged Erythrocytes
Technical Challenges of Leukocyte Collections

PRODUCT

• Efficiency of collection
  – Centrifugal separation technology limitations
  – Mobilization/production of target cell population within the donor or patient

• Purity of product
  – Target cells vs. unwanted cells
Technical Challenges of Leukocyte Collections

RECIPIENT

- Sterility and Potency of Product
- ABO compatibility
- Other transfusion reactions
- Infectious Disease Risk
- Unknown risks
Challenges of Leukapheresis

• Patient/Donor:
  – Venous access
  – Anticoagulation

• Regulatory requirements
  – Screening & Eligibility
  – Labeling

• Utilization of Resources
  – Staffing considerations
  – Competency standards
Challenges: Venous Access

- Minimal risk to patient/donor
  - Benefit of the procedure > risk of venous access
- Types to consider:
  - peripheral venous vs. central venous

Goal = Select Lowest risk

Best choice for a patient/donor may change over time
Peripheral Veins
Short term, single use

• Advantages:
  – Safest, fewest complications
  – Easy
  – Fastest

• Disadvantage:
  – Painful to patient/donor
  – Not all patients/donors have adequate veins for apheresis use
  – temporary
Central Vascular Access

- Permanent or temporary Catheter
- **Dual Lumen**
- Preferably hemodialysis or apheresis type catheter
- Large-bore lumens to provide flow rates ≤ 150 ml/min*

*Dialysis - 300 ml per minute DOQI guidelines)
** Flow Rate depends on type of proc.
COMPARISON OF VENOUS ACCESS IN TWO DIFFERENT DONOR GROUPS UNDERGOING MONONUCLEAR CELL (MNC) COLLECTION USING APHERESIS

Maria Cencerrado, RN, Christina Anderson, RN, BSN, HP, Christopher Edmond, RN, BSN, Joan Myers, RN, BSN, HP, Geeta Paranjape, MD and Laurie Sutor, MD

Abstract compares peripheral venous access between healthy donor group for matched unrelated stem cell transplants to male donors who have prostate cancer who are donating for themselves for their own cancer vaccine.
Magic words: dual lumen, large bore, dialysis-type central venous catheter
Anticoagulation

ACD-A (Acid citrate dextrose formula A)

- Most frequently used type
- + Extracorporeal Anticoagulant
- Majority gets returned! ONLY TPE
- MOA = binds ca++ in bloodstream
- Metabolized in minutes*
- Monitor patient/donor for hypocalcemia
- Interventions for hypocalcemia
  - Prophylactic Ca++ replacement is not always needed
Anticoagulation

- **Heparin**
  - Minor role in apheresis
    - Does not allow for good separation of blood
    + Limited role in pediatric apheresis
  - Systemic Anticoagulant
    - But can be reversed

- **ACD-A + Heparin**
  Limited use in leukocyte collections using apheresis

- **Trisodium Citrate + Hespan**
  Used in granulocyte collections to increase efficiency of collection (sedimenting agent)
Side Effects of Leukapheresis

PATIENT

+ blood

+ anticoagulant

MACHINE

- Desired component removed

+ Replacement Fluid

= Procedure Completed
Side Effects

DONOR/PATIENT

• Side effects from procedure
  – Replacement fluid
  – Citrate Toxicity
  – Hetastarch

• Side effects of pharmacologic stimulation: Neupogen, Corticosteroids

• Cellular loss
Side Effects

DONOR/PATIENT

• Fluid Balance challenges
  Hypervolemia  ---  Hypovolemia possible

• Vasovagal event
  – anxiety, need to void, fear of needles

• Venous access complications

• Symptoms: hypertension, hypotension, tachycardia, bradycardia, cardiac arrhythmias, difficulty breathing, sob, flushing, fever, diaphoresis, dizziness, fainting, muscle spasms, tetany, seizures, etc
Regulatory Requirements of Biological Product Collections

• Guidelines versus Regulations
Challenges of Regulations and Standards

- Screening differences among patient and donor groups
- Determining Infectious disease risk
  - Drawing IDM’s and Health History Screening
- Labeling requirements
  - ISBT
  - Conditions on degree of product risk
- Constant state of change!
Resource Utilization

Therapeutic services versus collection procedures

• Allocation of resources
  – Interdepartmental resources
  – Departmental resources: IS, QA, RADE, MA, ED, HPC lab, Mobile Staging
Resource Utilization: Staffing

- Availability of staff to perform procedures
  - Daily coverage to include TA & out of town contracts
  - Weekend support
  - Some scheduled; some urgent or add-ons

- Training and competency needs
  - Upon hire, annually, and as SOP’s change
  - Some procedures: frequent
  - Others are rare
Resource Utilization: Staffing

• Staff Support
  – Management team and Medical Directors
  – Mobile staging

• Credentials of apheresis operators
  + Apheresis Technicians
  + Apheresis Nurses
  + Hemapheresis Practitioners
Resource allocation for Leukocyte collections

• Pre-procedure workup (donor prescreen)
  – Medical clearance / donor eligibility
  – Assessment of venous access

• Administrative time: Paperwork & Inventory management

• Quality Assurance
  – Internal Audits
  – Inspections
  – Certification
Future Directions

• Gene Therapy
• Dendritic Cells
  – Prostate cancer
  – breast cancer
  – bladder cancer
  – malignant melanoma
• Immune modulation
Tricks of the trade…

• Call on all resources
  + ASFA
  + AABB
  + Manufacturers

• Technical considerations
  + machine specific
  + Photopheresis easy

• Regulatory considerations
  – FDA & Recipient concerns

• Competency and Support personnel
  – Competency is challenge
  – Donor procedures require a lot of extra internal support
CONCLUSIONS

DONOR APHERESIS

THERAPEUTIC APHERESIS

CELLULAR THERAPY
QUESTIONS?
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THANK YOU
Leukapheresis Procedures Defined

- Stem Cell collections (HPC)
- Lymphocyte collections (DLI's)
- Granulocyte collections
- MNC collections
- Bone Marrow Processing
- Research leukocyte collections
Apheresis in the U. S.

• Approximately 400,000 Therapeutic procedures performed nationally per year.
  • 250,000 Therapeutic Plasma Exchanges (62%)
  • 115,000 Stem Cell Collections (28%)
    » Autologous and Allogeneic
  • 30,000 Cellular Depletions & other (7.5%)
    » WBC Depletions
    » Platelet Depletions
    » Photopheresis
    » RBC Exchange

* Information Provided Caridian BCT Marketing Department for 2008 figures
Components of THERAKOS Photopheresis Treatment

Photopheresis or Extracorporeal Photopheresis (ECP)